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The Western Journal of Medicine

VOLUME 138 • NUMBER 1 JANUARY 1983

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Because uropathogens on vaginal cells...

New *in vitro* studies indicate specific *E.coli* receptors on the urogenital epithelium may be an important factor in recurrent infection.

Researchers have recently identified a chemical receptor for *E. coli* on the uroepithelial cells of women who are subject to recurrent urinary tract infections.[1]

The receptor is a glycosphingolipid known as α-D-Gal*p* (1→4)-β-D-Gal*p*. This carbohydrate is an antigen found on the red blood cells and the uroepithelial cells of women who have P-positive phenotypes.[1,2] It is *not* present on the erythrocytes or uroepithelial cells of women who are P-negative. Women who belong to the rare P-negative blood group had a much lower capacity for binding uropathogenic *E. coli* to their urogenital cells *in vitro* and had never experienced recurrent urinary tract infection. The cells from P-positive women, on the other hand, had a very high capacity for binding virulent *E. coli*. These women are generally much more likely to get recurrent infections. The chemical receptor appears to be a major factor responsible for this.[1]

Adherence of *E.coli* to vaginal mucosal cells increases susceptibility to urinary infections.

Another study, comparing women who experienced three or more urinary tract infections per year with healthy controls, found that vaginal cells from the women with recurrent urinary infections had a greater tendency to bind *E. coli in vitro*—even when the cells were cultured while there was no infection. The researchers speculated that deficient host defense mechanisms in vaginal mucosal cells may be responsible for recurrent urinary infections in many women.[3] *E. coli* and other uropathogens may colonize the vaginal introitus, adhere to receptors on mucosal cells and then infect the urinary tract.

Get to the source of recurrent urinary tract infection* with

*Due to susceptible organisms such as *E. coli, Klebsiella-Enterobacter* and *Proteus* species.

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CAPOTEN® TABLETS
Captopril Tablets

INDICATIONS: Hypertension — Because serious adverse effects have been reported (see WARNINGS), CAPOTEN is indicated for treatment of hypertensive patients who on multidrug regimens have either failed to respond satisfactorily or developed unacceptable side effects.

Heart Failure: CAPOTEN (captopril) is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.

WARNINGS: Proteinuria — Total urinary proteins >1 g/day were seen in 1.2% of patients on captopril; the nephrotic syndrome occurred in about ¼th of these cases. About 60% of affected patients had evidence of prior renal disease; the remainder had no known renal dysfunction. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients.

Membranous glomerulopathy was found in nearly all the proteinuric patients on captopril who were biopsied and may be drug related. Most cases of proteinuria occurred by the 8th month of therapy. Patients should have urinary protein estimates (dip-stick on 1st morning urine, or quantitative 24-hr urine — the latter provides greater precision when proteinuria is persistent and/or at low levels) before therapy, at approx. monthly intervals for the 1st 9 months of therapy, and periodically thereafter. For patients who develop proteinuria >1 g/day, or increasing proteinuria, the benefits and risks of continuing captopril should be evaluated.

Neutropenia/Agranulocytosis — Neutropenia (<300/mm³) associated with myeloid hypoplasia (probably drug related) occurred in about 0.3% of captopril treated patients. About half of the neutropenic patients developed systemic or oral cavity infections or other features of agranulocytosis. Most of the neutropenic patients had severe hypertension and renal function impairment; about half had systemic lupus erythematosus (SLE), or another autoimmune/collagen disorder; multiple concomitant drug therapy was common, including immunosuppressive therapy in a few cases. Daily doses of captopril in the leukopenic patients were relatively high, particularly in view of their diminished renal function. The neutropenia appeared 3 to 12 weeks after starting captopril; it developed relatively slowly, taking 10 to 30 days to have white blood count fall to its nadir; neutrophils returned to normal in about 2 weeks (other than 2 patients who died of sepsis).

Use captopril with caution in patients with impaired renal function, serious autoimmune disease (particularly SLE), or who are exposed to other drugs known to affect the white cells or immune response. In patients at particular risk (as noted above), perform white blood cell and differential counts prior to therapy, at about 2-week intervals for about the 1st 3 months of therapy, and periodically thereafter.

The risk of neutropenia in patients who are less seriously ill or who receive lower dosages appears to be smaller. In these patients white blood cell counts should be performed every 2 weeks for the 1st 3 months of therapy, and periodically thereafter. Perform differential counts when leukocytes are <4000/mm³ or the pretherapy white count is halved. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat; fever); if infection is suspected, perform counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count <1000/mm³) withdraw captopril and closely follow the patient's course.

Hypotension — Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]).

In heart failure, where blood pressure was either normal or low, transient decreases in blood pressure >20% were recorded in about ½ the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

PRECAUTION: General: *Impaired Renal Function,* Hypertension — Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure — About 20% of patients develop stable elevations of BUN and serum creatinine >20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis* — A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis, due to decreased afterload reduction.

Surgery/Anesthesia — If hypotension occurs during major surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Drug Interactions: *Hypotension: Patients on Diuretic Therapy* — Precipitous reduction of blood pressure may occasionally occur within the 1st 3 hours after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretics and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy. Alternatively, provide medical supervision for at least 3 hours after the initial dose in hypertensive patients.

Agents Having Vasodilator Activity: In heart failure patients vasodilators should be administered with caution.

Agents Causing Renin Release — Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity — The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium — Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Usage in Pregnancy: There are no adequate and well-controlled studies in pregnant women. Embryocidal effects were observed in rabbits. Therefore, captopril should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Nursing Mothers: Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age. Dosage, on a weight basis, was comparable to that used in adults. Captopril should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving about 4000 patients.

Renal — One to 2 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic — Neutropenia/agranulocytosis occurred in about 0.3% of captopril treated patients (see WARNINGS). Two of these patients developed sepsis and died.

Dermatologic — Rash (usually mild, maculopapular, rarely urticarial), often with pruritus and sometimes with fever and eosinophilia, in about 10 of 100 patients, usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity have also been reported. Angioedema of the face, mucous membranes of the mouth, or of the extremities in about 1 of 100 patients — reversible on discontinuance of captopril therapy. One case of laryngeal edema reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular — Hypotension in about 2 of 100 patients. See WARNINGS (Hypotension) and PRECAUTIONS (Drug Interactions) for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia — About 7 of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, and paresthesias reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.

Altered Laboratory Findings: Elevations of liver enzymes in a few patients although no causal relationship has been established. Rarely cholestatic jaundice and hepatocellular injury with secondary cholestasis have been reported. A transient elevation of BUN and serum creatinine may occur, especially in volume-depleted or renovascular hypertensive patients. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN. Small increases in serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

OVERDOSAGE: Primary concern in correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: CAPOTEN should be taken one hour before meals. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function.

Consult package insert before prescribing CAPOTEN (captopril).

HOW SUPPLIED: Available in tablets of 25, 50, and 100 mg in bottles of 100, and in UNIMATIC® unit-dose packs of 100 tablets.

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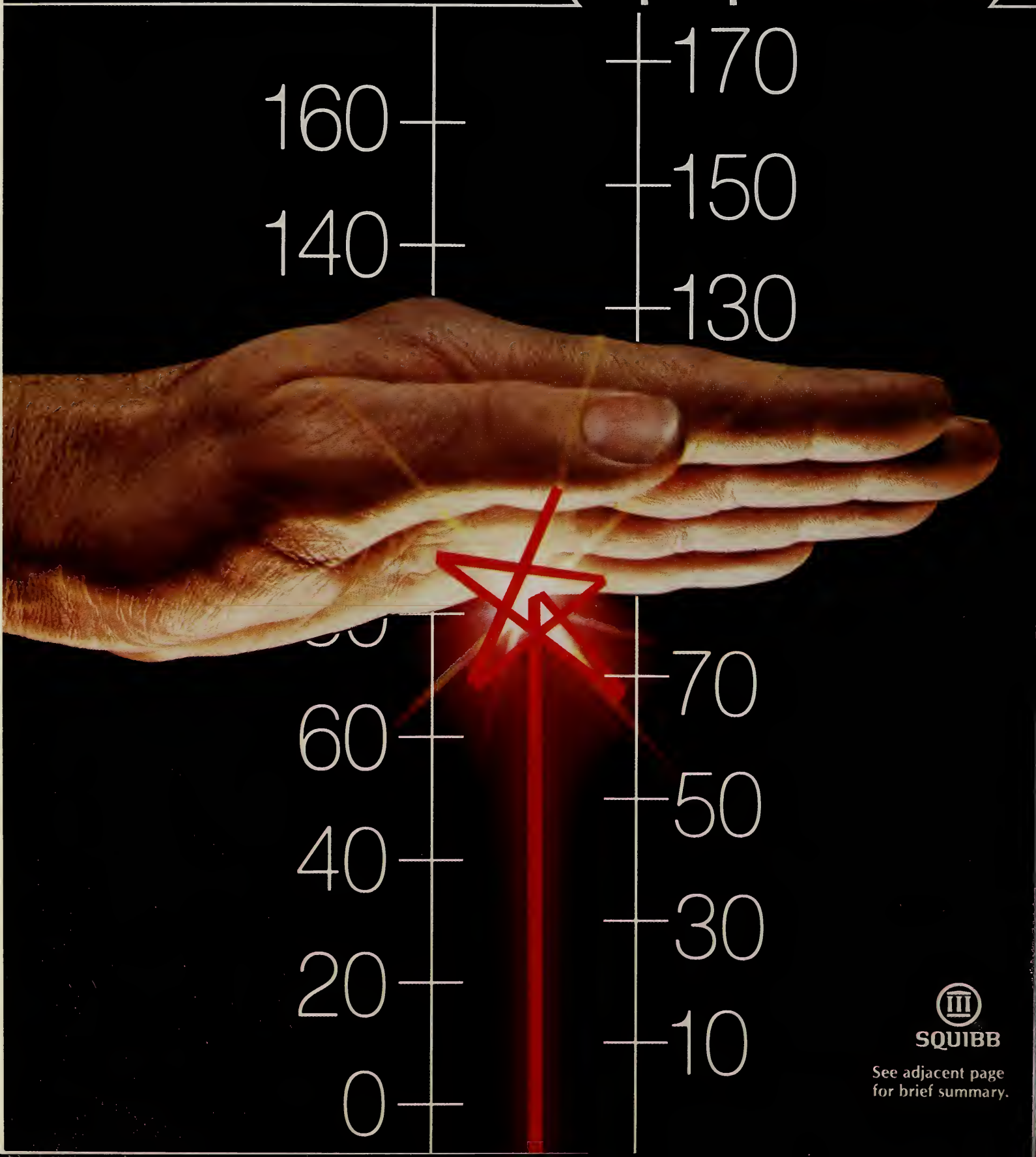

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Dr White is Professor of Medicine (Physiology) and Director, Physiological Research Laboratory, Scripps Institution of Oceanography, University of California, San Diego, La Jolla, California.

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CAPOTEN® TABLETS
Captopril Tablets

INDICATIONS: Hypertension — Because serious adverse effects have been reported (see WARNINGS), CAPOTEN is indicated for treatment of hypertensive patients who on multidrug regimens have either failed to respond satisfactorily or developed unacceptable side effects.

Heart Failure: CAPOTEN (captopril) is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.

WARNINGS: Proteinuria — Total urinary proteins >1 g/day were seen in 1.2% of patients on captopril; the nephrotic syndrome occurred in about ¼th of these cases. About 60% of affected patients had evidence of prior renal disease; the remainder had no known renal dysfunction. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients.

Membranous glomerulopathy was found in nearly all the proteinuric patients on captopril who were biopsied and may be drug related. Most cases of proteinuria occurred by the 8th month of therapy. Patients should have urinary protein estimates (dip-stick on 1st morning urine, or quantitative 24-hr urine — the latter provides greater precision when proteinuria is persistent and/or at low levels) before therapy, at approx. monthly intervals for the 1st 9 months of therapy, and periodically thereafter. For patients who develop proteinuria >1 g/day, or increasing proteinuria, the benefits and risks of continuing captopril should be evaluated.

Neutropenia/Agranulocytosis — Neutropenia (<300/mm³) associated with myeloid hypoplasia (probably drug related) occurred in about 0.3% of captopril treated patients. About half of the neutropenic patients developed systemic or oral cavity infections or other features of agranulocytosis. Most of the neutropenic patients had severe hypertension and renal function impairment; about half had systemic lupus erythematosus (SLE), or another autoimmune/collagen disorder; multiple concomitant drug therapy was common, including immunosuppressive therapy in a few cases. Daily doses of captopril in the leukopenic patients were relatively high, particularly in view of their diminished renal function. The neutropenia appeared 3 to 12 weeks after starting captopril; it developed relatively slowly, taking 10 to 30 days to have white blood count fall to its nadir; neutrophils returned to normal in about 2 weeks (other than 2 patients who died of sepsis).

Use captopril with caution in patients with impaired renal function, serious autoimmune disease (particularly SLE), or who are exposed to other drugs known to affect the white cells or immune response. In patients at particular risk (as noted above), perform white blood cell and differential counts prior to therapy, at about 2-week intervals for about the 1st 3 months of therapy, and periodically thereafter.

The risk of neutropenia in patients who are less seriously ill or who receive lower dosages appears to be smaller. In these patients white blood cell counts should be performed every 2 weeks for the 1st 3 months of therapy, and periodically thereafter. Perform differential counts when leukocytes are <4000/mm³ or the pretherapy white count is halved. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat; fever); if infection is suspected, perform counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count <1000/mm³) withdraw captopril and closely follow the patient's course.

Hypotension — Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]).

In heart failure, where blood pressure was either normal or low, transient decreases in blood pressure >20% were recorded in about ½ the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

PRECAUTION: General: *Impaired Renal Function*, Hypertension — Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure — About 20% of patients develop stable elevations of BUN and serum creatinine >20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis* — A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis, due to decreased afterload reduction.

Surgery/Anesthesia — If hypotension occurs during major surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Drug Interactions: *Hypotension: Patients on Diuretic Therapy* — Precipitous reduction of blood pressure may occasionally occur within the 1st 3 hours after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretics and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy. Alternatively, provide medical supervision for at least 3 hours after the initial dose in hypertensive patients.

Agents Having Vasodilator Activity: In heart failure patients vasodilators should be administered with caution.

Agents Causing Renin Release — Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity — The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium — Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Usage in Pregnancy: There are no adequate and well-controlled studies in pregnant women. Embryocidal effects were observed in rabbits. Therefore, captopril should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Nursing Mothers: Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age. Dosage, on a weight basis, was comparable to that used in adults. Captopril should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving about 4000 patients.

Renal — One to 2 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

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Cardiovascular — Hypotension in about 2 of 100 patients. See WARNINGS (Hypotension) and PRECAUTIONS (Drug Interactions) for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia — About 7 of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, and paresthesias reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.

Altered Laboratory Findings: Elevations of liver enzymes in a few patients although no causal relationship has been established. Rarely cholestatic jaundice and hepatocellular injury with secondary cholestasis have been reported. A transient elevation of BUN and serum creatinine may occur, especially in volume-depleted or renovascular hypertensive patients. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN. Small increases in serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

OVERDOSAGE: Primary concern in correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

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Consult package insert before prescribing CAPOTEN (captopril).

HOW SUPPLIED: Available in tablets of 25, 50, and 100 mg in bottles of 100, and in UNIMATIC® unit-dose packs of 100 tablets.

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Dr Harmon is Chairman, Department of Community Medicine, Maricopa County General Hospital; Director, Division of Public Health, Maricopa County Department of Health Services, Phoenix, and Adjunct Associate Professor, Department of Family and Community Medicine, University of Arizona, Tucson. Mr Turnipseed is Clinic Manager, Group Health Cooperative of Puget Sound, Seattle. Ms Schlittenhard is Administrative Services Manager of MEDEX Northwest, Seattle. Dr Penman is Medical Officer, Halls Creek, Australia.

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★ Affiliated Scientific Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.

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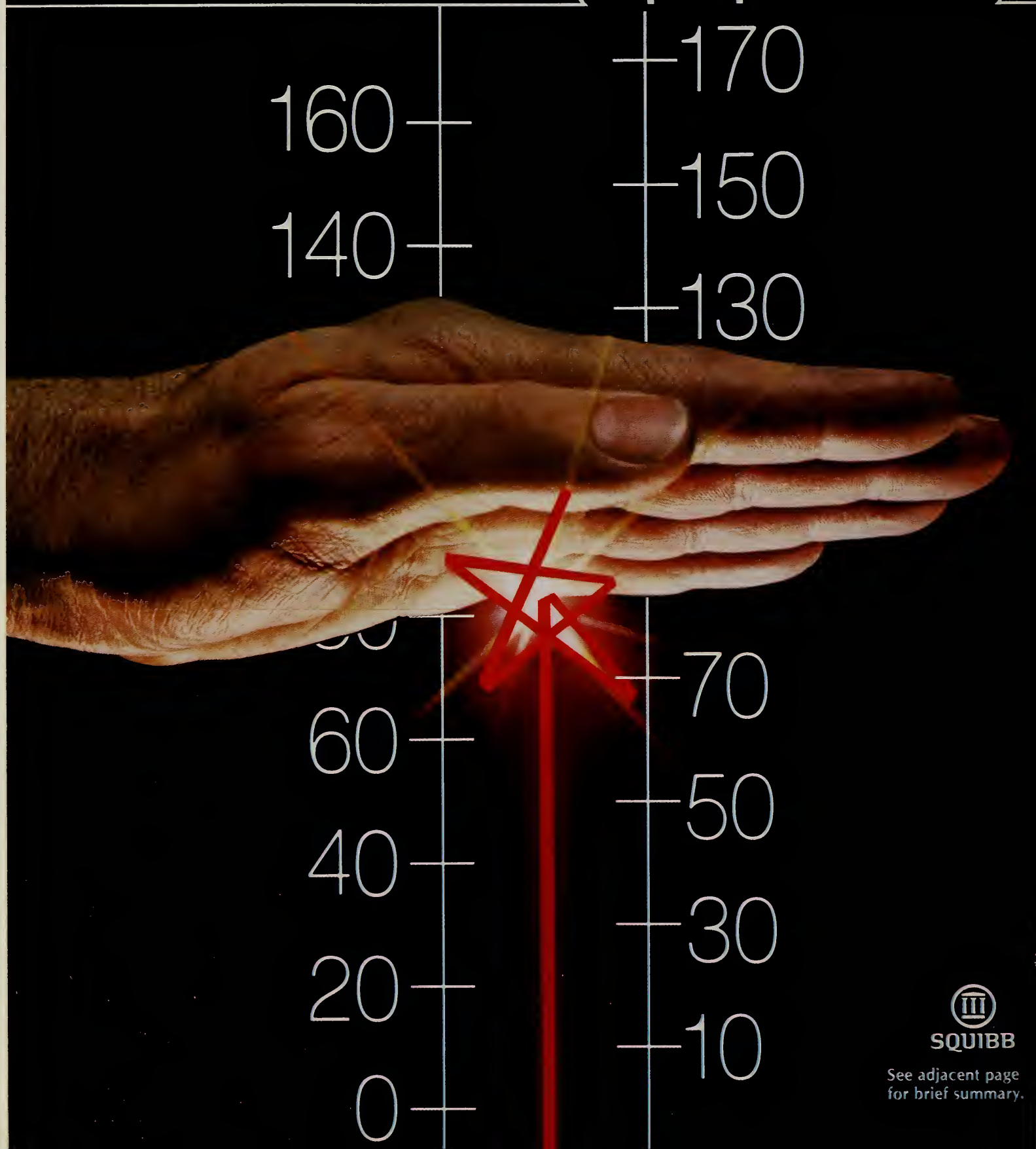

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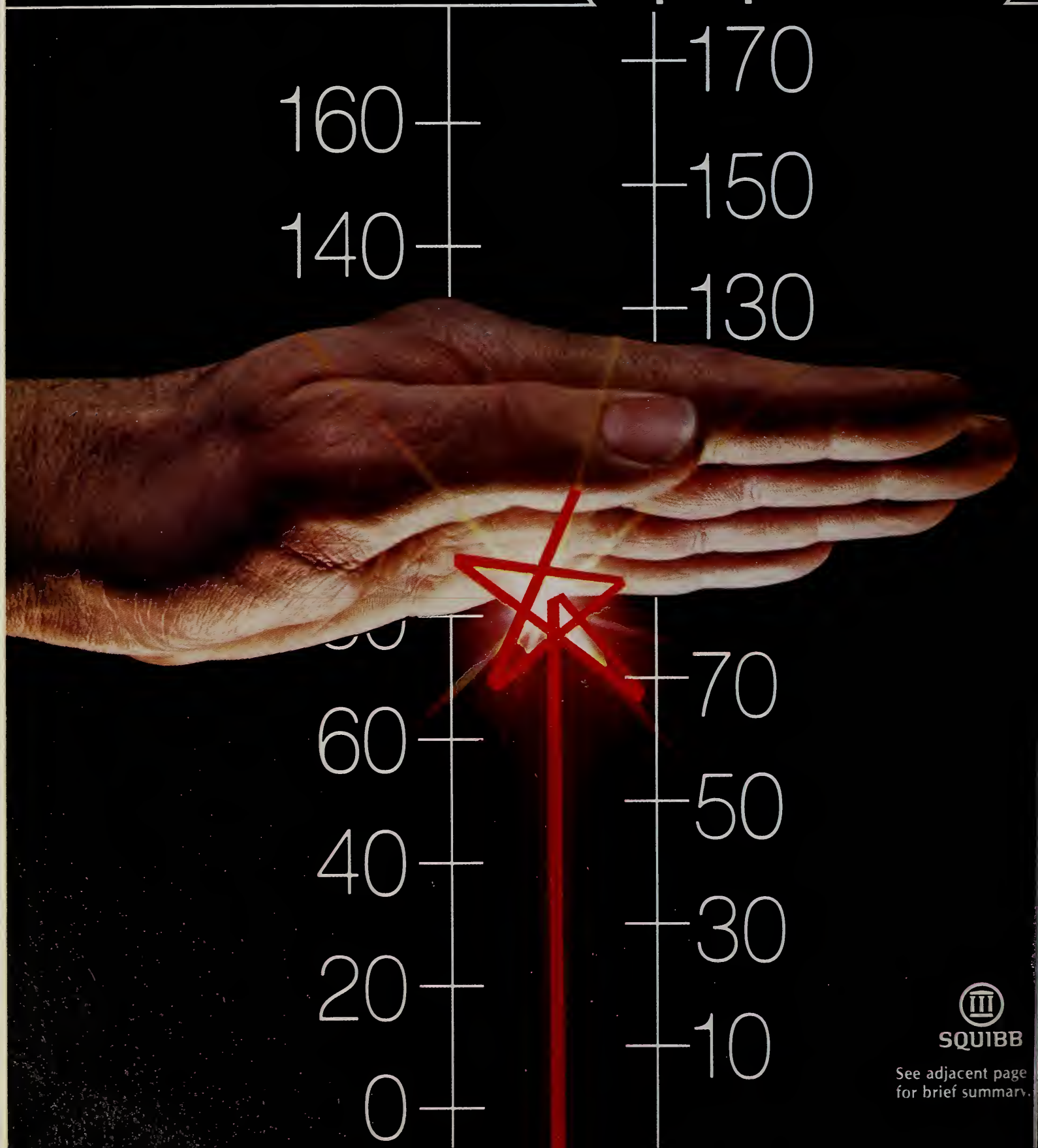

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CAPOTEN® TABLETS
Captopril Tablets

INDICATIONS: Hypertension — Because serious adverse effects have been reported (see WARNINGS), CAPOTEN is indicated for treatment of hypertensive patients who on multidrug regimens have either failed to respond satisfactorily or developed unacceptable side effects.

Heart Failure: CAPOTEN (captopril) is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.

WARNINGS: Proteinuria — Total urinary proteins >1 g/day were seen in 1.2% of patients on captopril; the nephrotic syndrome occurred in about ¼th of these cases. About 60% of affected patients had evidence of prior renal disease; the remainder had no known renal dysfunction. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients.

Membranous glomerulopathy was found in nearly all the proteinuric patients on captopril who were biopsied and may be drug related. Most cases of proteinuria occurred by the 8th month of therapy. Patients should have urinary protein estimates (dip-stick on 1st morning urine, or quantitative 24-hr urine — the latter provides greater precision when proteinuria is persistent and/or at low levels) before therapy, at approx. monthly intervals for the 1st 9 months of therapy, and periodically thereafter. For patients who develop proteinuria >1 g/day, or increasing proteinuria, the benefits and risks of continuing captopril should be evaluated.

Neutropenia/Agranulocytosis — Neutropenia (<300/mm³) associated with myeloid hypoplasia (probably drug related) occurred in about 0.3% of captopril treated patients. About half of the neutropenic patients developed systemic or oral cavity infections or other features of agranulocytosis. Most of the neutropenic patients had severe hypertension and renal function impairment; about half had systemic lupus erythematosus (SLE), or another autoimmune/collagen disorder; multiple concomitant drug therapy was common, including immunosuppressive therapy in a few cases. Daily doses of captopril in the leukopenic patients were relatively high, particularly in view of their diminished renal function. The neutropenia appeared 3 to 12 weeks after starting captopril; it developed relatively slowly, taking 10 to 30 days to have white blood count fall to its nadir; neutrophils returned to normal in about 2 weeks (other than 2 patients who died of sepsis).

Use captopril with caution in patients with impaired renal function, serious autoimmune disease (particularly SLE), or who are exposed to other drugs known to affect the white cells or immune response. In patients at particular risk (as noted above), perform white blood cell and differential counts prior to therapy, at about 2-week intervals for about the 1st 3 months of therapy, and periodically thereafter.

The risk of neutropenia in patients who are less seriously ill or who receive lower dosages appears to be smaller. In these patients white blood cell counts should be performed every 2 weeks for the 1st 3 months of therapy, and periodically thereafter. Perform differential counts when leukocytes are <4000/mm³ or the pretherapy white count is halved. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat; fever); if infection is suspected, perform counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count <1000/mm³) withdraw captopril and closely follow the patient's course.

Hypotension — Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]).

In heart failure, where blood pressure was either normal or low, transient decreases in blood pressure >20% were recorded in about ½ the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

PRECAUTION: General: *Impaired Renal Function,* Hypertension — Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure — About 20% of patients develop stable elevations of BUN and serum creatinine >20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis* — A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis, due to decreased afterload reduction.

Surgery/Anesthesia — If hypotension occurs during major surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Drug Interactions: *Hypotension: Patients on Diuretic Therapy* — Precipitous reduction of blood pressure may occasionally occur within the 1st 3 hours after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretics and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy. Alternatively, provide medical supervision for at least 3 hours after the initial dose in hypertensive patients.

Agents Having Vasodilator Activity: In heart failure patients vasodilators should be administered with caution.

Agents Causing Renin Release — Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity — The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium — Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Usage in Pregnancy: There are no adequate and well-controlled studies in pregnant women. Embryocidal effects were observed in rabbits. Therefore, captopril should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Nursing Mothers: Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age. Dosage, on a weight basis, was comparable to that used in adults. Captopril should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving about 4000 patients.

Renal — One to 2 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic — Neutropenia/agranulocytosis occurred in about 0.3% of captopril treated patients (see WARNINGS). Two of these patients developed sepsis and died.

Dermatologic — Rash (usually mild, maculopapular, rarely urticarial), often with pruritus and sometimes with fever and eosinophilia, in about 10 of 100 patients, usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity have also been reported. Angioedema of the face, mucous membranes of the mouth, or of the extremities in about 1 of 100 patients — reversible on discontinuance of captopril therapy. One case of laryngeal edema reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular — Hypotension in about 2 of 100 patients. See WARNINGS (Hypotension) and PRECAUTIONS (Drug Interactions) for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia — About 7 of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, and paresthesias reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.

Altered Laboratory Findings: Elevations of liver enzymes in a few patients although no causal relationship has been established. Rarely cholestatic jaundice and hepatocellular injury with secondary cholestasis have been reported. A transient elevation of BUN and serum creatinine may occur, especially in volume-depleted or renovascular hypertensive patients. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN. Small increases in serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

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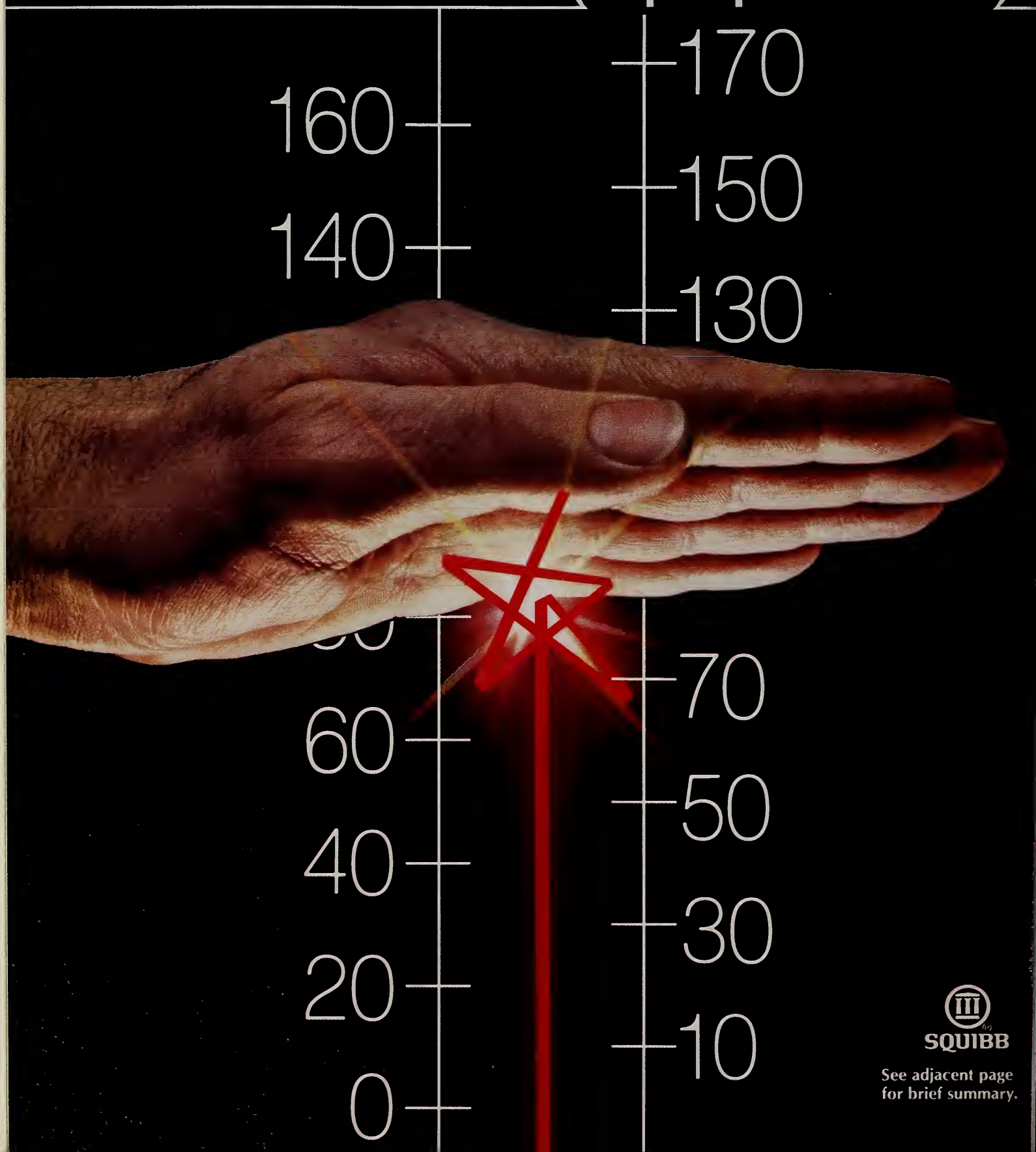

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Dr Bodey is Professor of Medicine and Chief of Chemotherapy and Infectious Diseases, Department of Developmental Therapeutics, The University of Texas System Cancer Center, Texas Medical Center, Houston.

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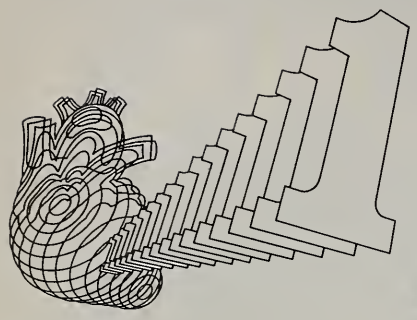
The only once-a-day beta-blocker for both hypertension and angina pectoris



CORGARD®
nadolol tablets

40 mg, 80 mg, 120 mg, 160 mg scored tablets

CORGARD® TABLETS
Nadolol Tablets

DESCRIPTION: Corgard (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.

CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure—Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery — Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Hepatic or Renal Function — Use nadolol with caution in presence of either of these conditions (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.

Drug Interactions — Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. When treating patients with nadolol plus a catecholamine-depleting agent, carefully observe for evidence of hypotension and/or excessive bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility — In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy — In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus.

Nursing Mothers — It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when nadolol is administered to a nursing woman. Animal studies showed that nadolol is found in the milk of lactating rats.

Pediatric Use — Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular — Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System** — Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory** — Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal** — Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous** — Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

Potential Adverse Effects: Although other adverse effects reported with other beta-adrenergic blocking agents have not been reported with nadolol, they should be considered potential adverse effects of nadolol. **Central Nervous System** — reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal** — mesenteric arterial thrombosis; ischemic colitis. **Hematologic** — agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic** — fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous** — reversible alopecia; Peyronie's disease; erythematous rash.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia — Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension — Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm — Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 80 to 240 mg q.d. (most patients respond to 160 mg or less daily). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 80 to 320 mg q.d. (rarely, doses up to 640 mg may be needed).

Patients with renal failure require adjustment in dosing interval — see package insert for dosage in these patients.

For full prescribing information, consult package insert.

HOW SUPPLIED: In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100 and 1000 tablets and in Unimatic® unit-dose packs of 100 tablets. The 40 mg and 80 mg tablets are also available in convenience packages containing 4 blister cards of 7 tablets each.

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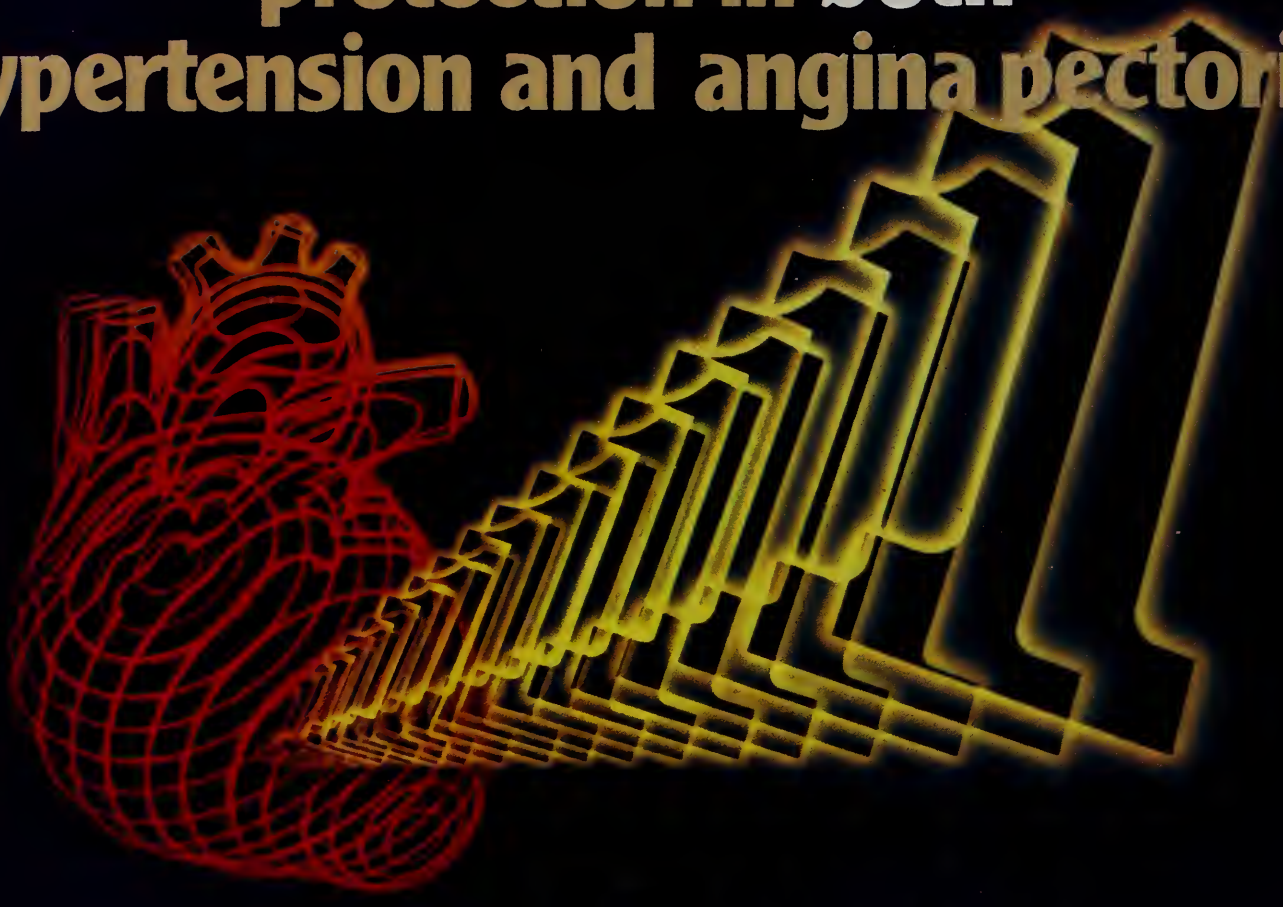
Only one beta-blocker provides once-a-day round-the-clock protection in both hypertension and angina pectoris.



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The Western Journal of Medicine

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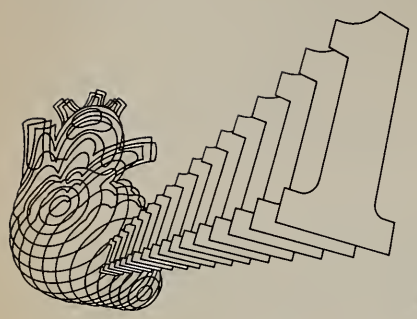
The only once-a-day beta-blocker for both hypertension and angina pectoris



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Nursing Mothers — It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when nadolol is administered to a nursing woman. Animal studies showed that nadolol is found in the milk of lactating rats.

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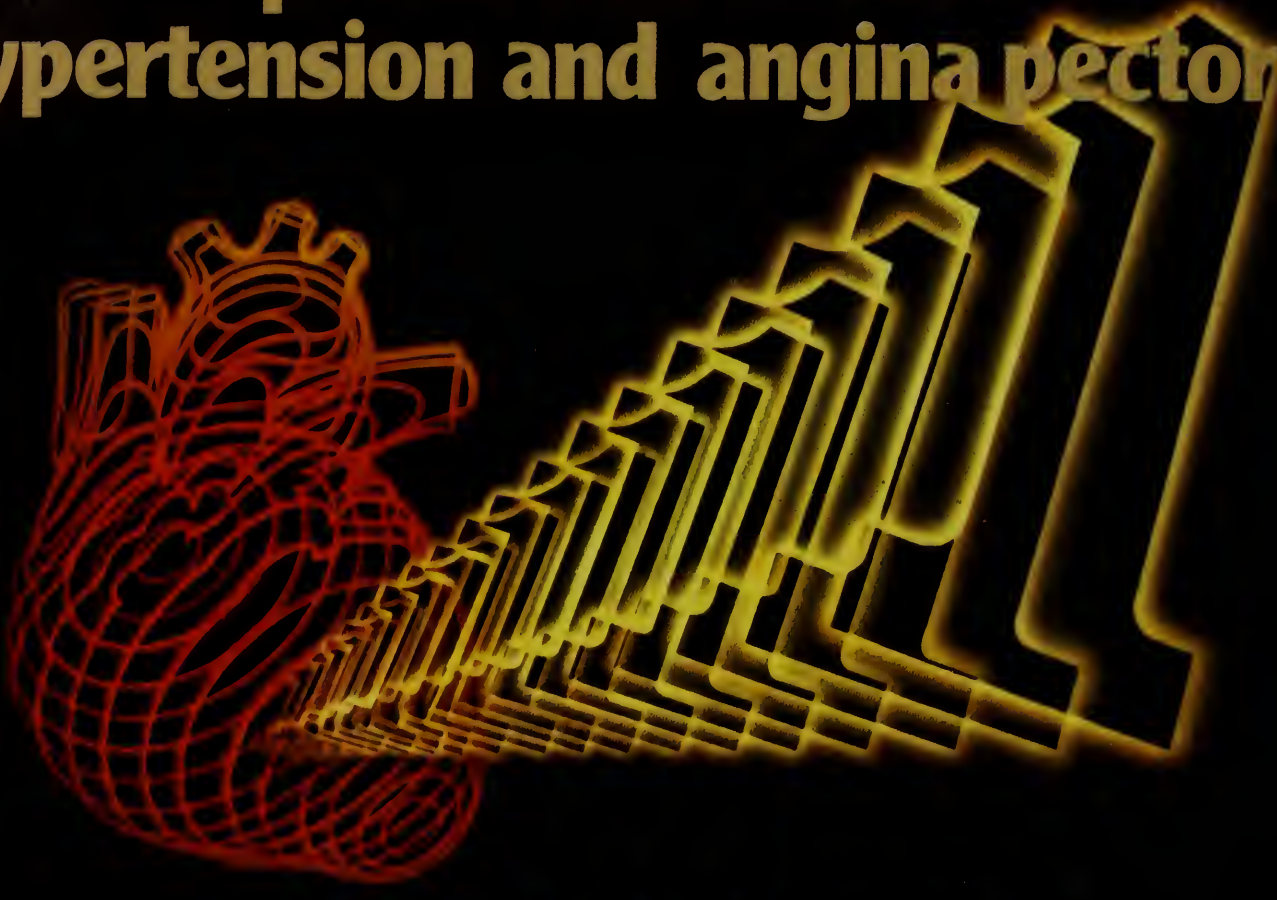

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Colchicine Use for Familial Mediterranean Fever

Observations Associated With Long-term Treatment

ROBERT S. PETERS, MD, *Fresno, California;* THOMAS J. A. LEHMAN, MD, *Bethesda, Maryland, and* ARTHUR D. SCHWABE, MD, *Los Angeles*

Of 85 patients with familial Mediterranean fever receiving continuous prophylactic colchicine therapy, 62 (73 percent) have had a significant reduction in the severity and frequency of their attacks. All 62 have been observed for three years or more, for a total of 4,680 patient-months and a mean duration of 75.5 months. Of the 85 patients, 23 (27 percent) did not complete three years of treatment for a variety of reasons. Diarrhea was the most common side effect, necessitating reduction of colchicine dosage in 12 patients, but discontinuation of treatment in only one. No other significant side effects were observed. Continuous, prophylactic colchicine therapy is effective in preventing the recurrent febrile paroxysms of familial Mediterranean fever and is indicated in those patients who are incapacitated by frequent attacks or who are at risk for amyloidosis developing.

The efficacy of prophylactic, continuous colchicine therapy in preventing the recurrence of febrile attacks of familial Mediterranean fever was established by three controlled studies in 1974[1-3] and later confirmed by reports from several centers.[4-6] Between the years 1967 and 1978 a total of 99 patients with familial Mediterranean fever from the clinics of two California hospitals were selected to receive continuous colchicine therapy. The subsequent course of these patients, including adherence to the recommended regimen, dosage and side effects, and the long-term efficacy of the treatment in preventing attacks, constitutes the basis of this report.

Methods

The diagnosis of familial Mediterranean fever in all patients in this study was based on established criteria.[4,7] The 99 patients included 62 Armenians, 30 Jews and 7 of other ethnic origin. There were 56 male and 43 female patients, ranging in age from 4 to 64 years. Indications for administering continuous colchicine therapy were one or more of the following: frequent, severe attacks significantly interfering with a normal pattern of life; failure of alternative therapy, and a family history of familial Mediterranean fever amyloidosis. The patients were informed of the indications for colchicine therapy, possible side effects and potential benefits. Patients with a reproductive potential were also advised to interrupt the colchicine therapy before a planned conception. Initially, a dosage of 0.5 or 0.6 mg of colchicine twice a day was recommended, but the dosage was increased to 0.6 mg three times a day for all patients older than 16 years of age in 1974.

Patients were observed at regular intervals and questioned about adherence to the regimen, symptoms, frequency of attacks and side effects. A physical examination and a qualitative test for urine protein were carried out at each visit. Routine blood counts were done before

Refer to: Peters RS, Lehman TJA, Schwabe AD: Colchicine use for familial Mediterranean fever—Observations associated with long-term treatment. West J Med 1983 Jan; 138:43-46.

From the Departments of Medicine, UCLA School of Medicine, Los Angeles, and Valley Medical Center of Fresno; and the Department of Pediatrics, University of California, San Diego.

Dr Lehman, formerly with the Department of Pediatrics, University of California, San Diego, is now affiliated with the National Institute of Arthritis, Digestive and Kidney Diseases, Bethesda, Maryland.

Submitted April 29, 1982.

Reprint requests to Arthur D. Schwabe, MD, Department of Medicine, UCLA School of Medicine, Los Angeles, CA 90024.

and at the time of two or more subsequent monthly clinic visits.

Results

Duration of Treatment

The course of the 99 patients originally entered in the study is outlined in Table 1. Two patients died of causes unrelated to familial Mediterranean fever or treatment and 12 were lost to follow-up. Of the remaining 85 patients available for analysis, 62 (73 percent) have continued to take colchicine for three or more years. The mean duration of treatment as of April 1981 was 75.5 months, with a range of 36 to 169 months (Figure 1). A total of 42 patients have completed five or more years of continuous colchicine therapy.

Of the 85 patients 23 (27 percent) interrupted, discontinued or were withdrawn from therapy for reasons shown in Table 1 and detailed later in this report. Eight patients—who were apprehensive about the possible side effects of colchicine—used the drug sporadically or discontinued using it entirely and were therefore classified as noncompliant. One patient was withdrawn from colchicine therapy due to chronic diarrhea that became intractable when quinidine had to be added to his regimen because of a coexistent arrhythmia. In a second patient, a 44-year-old man who had been successfully treated for more than five years, was advised to interrupt therapy when he decided to start a family. These three patients did not complete the prescribed course of therapy because of actual, presumed or potential side effects.

TABLE 1.—*A Long-term Study of Colchicine Therapy for Familial Mediterranean Fever Showing Degree of Compliance to Recommended Regimen*

Description of Patients	*No.*	*No. (percent)*
Entered in study		99
Removed from study		14
Died (unrelated to FMF)	2	
Lost to follow-up	12	
Followed regularly		85 (100)
Did not complete full course of therapy		23 (27)
Did not comply with regimen	8	
Therapy withdrawn because of side effects	3	
Failed to respond to colchicine	12	
Completed >3 years of therapy		62 (73)

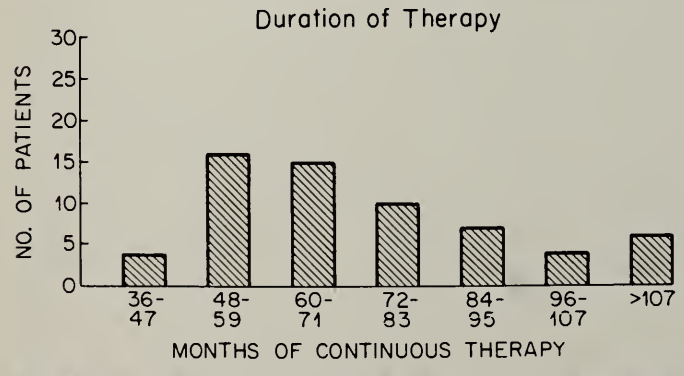

Figure 1.—Duration of continuous, daily colchicine treatment in 62 patients with familial Mediterranean fever.

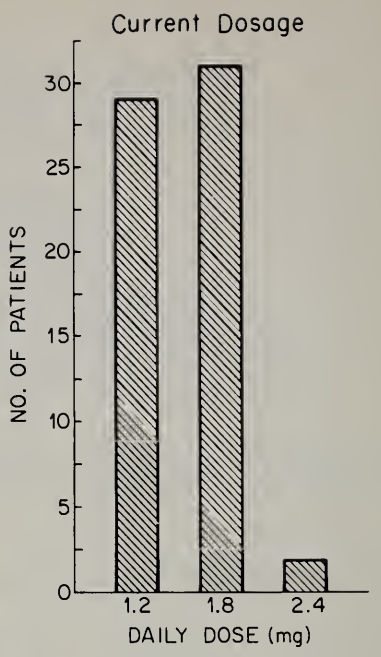

Figure 2.—Current daily colchicine dosage in 62 patients with familial Mediterranean fever on long-term treatment.

Eight patients with coexistent functional or psychological disorders continued to have a variety of symptoms, such as chronic abdominal pain, weakness and headaches, which were unaffected by taking colchicine. In three patients who were found to be addicted to narcotics and who continued to complain of symptoms, neither the efficacy nor the adherence to the prescribed regimen could be verified. An additional patient reported no change in the frequency and severity of his attacks while taking colchicine. These 12 patients were classified as treatment failures (Table 1).

Dosage of Colchicine

From 1967 to 1974 patients were maintained on a regimen of 1.0 to 1.2 mg of colchicine per day. Subsequently, however, a dosage of 1.8 mg (0.6 mg three times a day) was prescribed for all adults entering the study for optimal suppression of attacks. The effects of familial Mediterranean fever were controlled in six children with the administration of 1.2 mg a day. The dosage was reduced to 1.2 mg a day in 22 adult patients. Reduction was necessitated in 12 patients due to side effects, which will be detailed later in this report. The other ten patients voluntarily reduced their dosage on advice from other family members or friends who were doing well on a lower dosage, or because they forgot to take the midday dose and seemed to notice no ill effect. No patients were maintained on less than 1.2 mg a day. The colchicine dosage was increased to 2.4 mg a day in two patients whose attacks were partially, but not completely, suppressed on the lower dosage. The

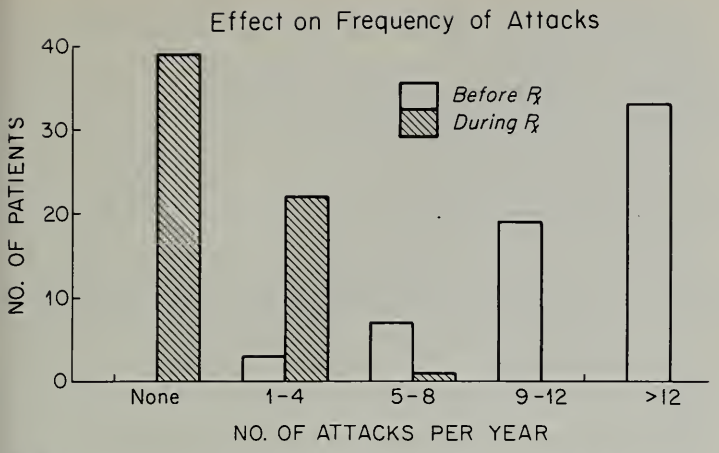

Figure 3.—Long-term effect on the frequency of attacks of familial Mediterranean fever in 62 patients taking daily, prophylactic colchicine.

amount of colchicine currently taken by the 62 patients is shown in Figure 2.

Effect of Colchicine Therapy on Attacks

All of the 62 (73 percent) patients still receiving colchicine therapy in April 1981 had a significant reduction in the severity and frequency of their attacks, as shown in Figure 3. In all, 39 patients ceased to have attacks for the period of study—that is, more than three years—and 22 patients had only one to four attacks a year. None of the treated patients required hospital admission for familial Mediterranean fever during the period of treatment. This attack frequency is in sharp contrast to the number of attacks occurring before the institution of therapy.

Of the 85, there were 23 (27 percent) who failed to complete three years of therapy or had terminated therapy before April 1981 for the reasons previously mentioned. Although several of these patients clearly benefited from taking the drug, all were considered long-term treatment failures. It should be stressed, however, that for patients with familial Mediterranean fever, treatment requires a flexible, multifaceted approach that takes into account the tendency of addiction to narcotics, the coexistence of other physical and emotional disorders and the concern about long-term side effects of colchicine use and its potential harmful effects on conception. Any of these problems may result either in noncompliance or failure of colchicine therapy.

Side Effects

Virtually all patients had mild, transient diarrhea and abdominal discomfort for one to three days after the institution of treatment. However, 13 patients continued to have two to four loose or watery bowel movements a day for more than a month. In 6 of the 13 patients, reducing the colchicine dosage from 1.8 to 1.2 mg a day resulted in a return to normal bowel habits. The other seven patients did not improve with reduction in drug dosage alone. Two of them responded to the addition of a psyllium seed preparation and a third to the administration of diphenoxylate hydrochloride with atropine. Three patients continued to have increased frequency of bowel movements, but prefer this side effect to recurrent attacks of familial Mediterranean fever. The 13th previously cited patient with intractable diarrhea after the addition of quinidine had to be withdrawn from colchicine therapy.

In four patients transient, self-limited anorexia and nausea developed, but no vomiting. No weight loss, weakness, myopathy, hair loss, abortions, anemia, leukopenia or steatorrhea was observed in any of the patients. Small intestinal biopsies are being carried out in a number of the patients; preliminary results do not indicate any significant histologic abnormalities. Except for one patient mentioned previously, no one reported libidinal disturbances or infertility. None of the women or sexual partners of the men in this study became pregnant during the study period.

Discussion

During the past seven years continuous, prophylactic colchicine therapy has significantly improved the management and prognosis of patients with familial Mediterranean fever.[1-6] The long-term follow-up study presented here shows not only that this form of treatment continues to be effective, but also that it is relatively free of significant side effects. Administration of the drug had to be discontinued in only one patient because of intractable diarrhea.

In dosages of more than 1.8 mg a day colchicine may cause malabsorption of fat, D-xylose and vitamin B_{12}, as well as inhibition of intestinal enzymes,[8,9] complications not observed in our patients. In even larger doses, colchicine may be toxic to gastrointestinal mucosa, bone marrow, kidneys, lungs and cardiovascular system.[10-12] Such severe toxicity, however, occurs most often after accidental overdoses or suicide attempts in patients who have received 7 to 350 mg of colchicine in relatively short periods of time.[13] The relative safety of recommended daily dosages of colchicine (that is, 1 to 1.8 mg) has been emphasized in other articles.[5,14] Nevertheless, we continue to be concerned about the effect of colchicine on fertilization, implantation and pregnancy and advise our patients to stop taking the drug three months before planned conception.

Wright and co-workers[15] found that three of five patients who had premonitory symptoms could abort an attack by taking 6 mg of colchicine in divided doses over 72 hours. This intermittent therapy is difficult for most patients. Many cannot clearly recognize the earliest signs of an attack and wait until the attack is well established and no longer amenable to colchicine suppression. Others start taking colchicine for unrelated symptoms, especially upper respiratory tract infections and functional abdominal pain, and wrongly conclude that the drug is totally ineffective. Another strong argument for continuous colchicine therapy is its possible beneficial effect on amyloidosis. Early evidence suggests

that colchicine therapy may prevent, reverse or impede the progression of amyloidosis.[14,16] At present, therefore, there is little question that those ethnic groups at high risk for amyloidosis developing should be receiving continuous colchicine therapy.

Colchicine administration has been used with variable success in several other clinical disorders such as gout, pseudogout, Behçet's disease, necrotizing vasculitis, scleroderma and Paget's disease, but little is known about its mechanism of action. Although interference with microtubule formation, degranulation of neutrophils and alteration of leukocyte adenosine 3′:5′-cyclic phosphate levels have been found in vitro, the relevance of these effects to colchicine prophylaxis for familial Mediterranean fever is unclear.[17,18]

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Medical Practice Questions

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Transcutaneous Electrical Nerve Stimulation (TENS) and Percutaneous Electrical Nerve Stimulation (PENS) and Electroacutherapy

QUESTIONS:

Has the use of transcutaneous electrical nerve stimulation (TENS) *or percutaneous electrical nerve stimulation* (PENS) *for the relief of pain become accepted medical practice, or are they investigational?*

Is it accepted medical practice to use electroacutherapy modalities in conjunction with either transcutaneous electrical nerve stimulation or percutaneous stimulation?

OPINION:

In the opinion of the Advisory Panels on Internal Medicine, Neurology, Neurosurgery and Physical Medicine and Rehabilitation, transcutaneous electrical nerve stimulation (TENS) and percutaneous electrical nerve stimulation (PENS) have been accepted as established therapeutic modalities for the relief of pain. TENS is acceptable treatment for acute as well as chronic pain, primarily of musculoskeletal or neurological etiology. PENS is also acceptable treatment but because of associated risks it should be reserved for chronic, intractable pain conditions.

Electroacutherapy modalities used in conjunction with either TENS or PENS for relief of pain are not established medical practice. Further investigation is required to determine their safety and efficacy in patients with pain syndromes or other conditions. Such research should be carried out under a strict scientific protocol.

Branhamella catarrhalis Pneumonia

MILTON H. LOUIE, MD; ELIZABETH L. GABAY, MD; GLENN E. MATHISEN, MD, *and* SYDNEY M. FINEGOLD, MD, *Los Angeles*

The diagnosis of Branhamella catarrhalis *pneumonia in five cases was established by culture of pulmonary secretions obtained by transtracheal aspiration.* B catarrhalis *caused an acute lobar pneumonia which usually responded promptly to appropriate antimicrobial therapy. Recognition that this organism may cause pneumonia in a nonimmunocompromised person should alert clinicians to consider it as a possible pathogen when Gram-negative diplococci are seen on smears of specimens from the lower respiratory tract.*

Branhamella catarrhalis, formerly *Neisseria catarrhalis,* has generally been regarded as a commensal of the upper respiratory tract flora. Recently, its recovery has been associated with exacerbations of chronic bronchitis.[1] It has been implicated as a cause of pneumonia in rare instances, usually in an immunosuppressed host and in patients with chronic obstructive lung disease.[2-4] We present our experience with five cases of pneumonia caused by *B catarrhalis.*

Patients and Methods

Between July 1977 and January 1981, all cases of pneumonia, community or nosocomially acquired, were reviewed by the Infectious Disease Section at the VA Wadsworth Medical Center, Los Angeles, as part of a pneumonia surveillance program. Four cases of pneumonia due to *B catarrhalis* were observed during this time. An additional case had occurred before the surveillance period.

Clinical and Laboratory Features

The clinical features of the cases are summarized in Table 1. All patients were men who had been admitted to the medical service. Symptoms of dyspnea and productive cough were present from one to four days before pneumonia was diagnosed. In three patients the sputum was blood-tinged or rusty in color. Two patients had pleuritic pain. Prodromal symptoms and symptoms of concomitant viral infection, such as myalgia and rhinorrhea, were not observed. All patients were febrile to 38.3°C (101°F), or higher, and had acute pneumonia. Roentgenograms of the chest showed alveolar and bronchopneumonic infiltrates. Pleural effusion and cavitation were not seen. In three cases the right lower lobe was involved; the right upper lobe and the left lower lobe were involved in one case each. Physical signs noted on examination varied from diffuse wheezes and rhonchi to localized signs of consolidation.

The diagnosis was established by culture of *B catarrhalis* from material obtained by transtracheal aspiration. Gram stain of these specimens showed polymorphonuclear leukocytes and Gram-negative diplococci. Gram-stained sputum smears of three of the cases were also reported to show polymorphonuclear cells and many Gram-negative diplococci. The diplococci were often found both intracellularly and extracellularly. Not uncommonly, it was initially suggested that these patients had pneumonia caused by *Neisseria meningitidis.*

Response to therapy was typically rapid, with defervescence and radiographic improvement occurring within 48 hours in four of our patients. The exception was one patient with concurrent legionnaires' disease. None of our patients had associated bacteremia, empyema, sinusitis, meningitis or endocarditis. All of them survived.

Selected Case Reports

Case 1 (Patient 4, Table 1). This 63-year-old alcoholic man was admitted to hospital in December 1978 with fever and productive cough of a few days' duration. Five days earlier he had sustained a fracture of the left humeral head. His temperature was 39°C (102.2°F) taken orally; he appeared malnourished. Examination of the chest showed an increased anteroposterior diameter with diffuse hyperresonance and rhonchi; diminished breath sounds and egophony were

Refer to: Louie MH, Gabay EL, Mathisen GE, et al: *Branhamella catarrhalis* pneumonia. West J Med 1983 Jan; 138:47-49.

From the Infectious Disease Section, Medical Service, Veterans Administration Wadsworth Medical Center, Los Angeles, and the Department of Medicine, UCLA School of Medicine, Los Angeles..

Submitted, revised, May 13, 1982.

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TABLE 1.—*Clinical Features of* Branhamella catarrhalis *Pneumonia*

Patient	Age, Sex	Date of Onset	Underlying Processes	Other Pathogens Isolated	Initial Leukocyte Count cells/μl	Physical Signs at Presentation				Drug Therapy
						T °C (°F)	Heart Rate beats/min	Respirations	Chest Findings	
1*	24 ♂	Jun 1975	Hypogammaglobulinemia	*Haemophilus influenzae*	18,800	39.1(102.4)	90	20	Diffuse rhonchi	Cefoxitin
2	72 ♂	Dec 1977	Congestive heart failure, COPD	None	15,900	38.3(101.0)	130	30	Localized rales, egophony, decreased breath sounds	Ampicillin
3	62 ♂	Mar 1978	Concurrent legionnaires' pneumonia†	None	18,600	39.4(103.0)	120	22	Localized rales, increased fremitus	Ampicillin, erythromycin
4	63 ♂	Dec 1978	Hemochromatosis, COPD, alcoholism	*H influenzae*	10,900	38.9(102.0)	110	18	Diffuse rhonchi, localized egophony and decreased breath sounds	Bacampicillin hydrochloride
5	28 ♂	May 1980	Systemic lupus erythematosus, renal insufficiency, prednisone/azathioprine therapy	None	22,000	39.1(102.4)	108	24	Diffuse wheezes, bilateral rales	Penicillin, erythromycin

COPD = chronic obstructive pulmonary disease; T = temperature.

*Previously described.[12]
†Documented serologically.

Figure 1.—Chest roentgenogram of patient 4 showing a right lower lobe infiltrate.

noted over the right lower lung. The chest roentgenogram is shown as Figure 1. Gram stain of a smear of transtracheal aspirate specimen showed many polymorphonuclear cells with large numbers of Gram-negative diplococci. A few Gram-negative coccobacillary forms were also noted. Culture of this material yielded a heavy growth of *B catarrhalis* and a moderate growth of *Haemophilus influenzae*. The patient received bacampicillin hydrochloride, 800 mg orally every 12 hours for ten days. Defervescence and a pronounced decrease in sputum production were noted after 48 hours of therapy. Another roentgenogram of the chest 12 days after admission to hospital showed only some mild right pleural thickening.

CASE 2 (Patient 5). This 28-year-old man with systemic lupus erythematosus and diffuse proliferative glomerulonephritis was being treated with azathioprine and prednisone before his admission to hospital. When seen he had poorly controlled hypertension and a four-day history of cough productive of blood-tinged sputum. The temperature was 39.1°C (102.4°F) taken orally. Examination of the chest showed diffuse wheezes and a few fine bilateral basilar rales. Serum creatinine was 6.6 mg per dl; blood urea nitrogen was 103 mg per dl. The chest roentgenogram done at the time of admission showed cardiomegaly, increased vascular markings and a bronchopneumonic right lower lobe infiltrate (Figure 2). Gram-stained smears of a sputum specimen and secretions obtained by transtracheal aspiration showed many polymorphonuclear leukocytes and Gram-negative diplococci. The patient was begun on a regimen of penicillin, 6 million units a day. He also received erythromycin initially because of the prevalence of

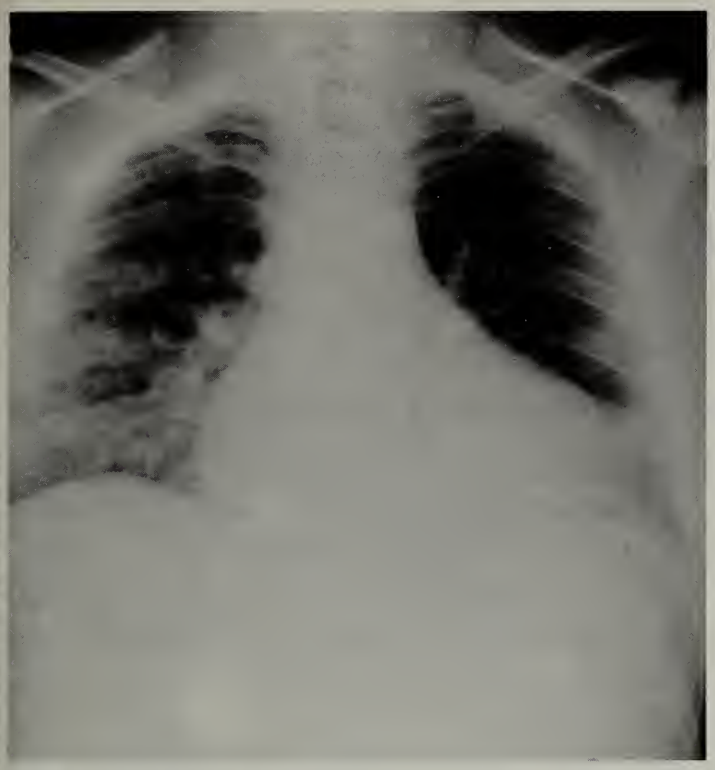

Figure 2.—Chest roentgenogram of patient 5 showing a bronchopneumonic infiltrate in the right lower lobe.

Legionella pneumonia in our hospital at that time. *B catarrhalis* was obtained from both sputum and transtracheal aspirate in pure culture. The patient's fever subsided rapidly and pulmonary infiltrate cleared after 48 hours of therapy.

Discussion

B catarrhalis appears as kidney-bean-shaped Gram-negative diplococci. Its microscopic morphology resembles that of the genus *Neisseria* from which it is genetically distinct. *B catarrhalis* forms gray-white nonchromogenic colonies that grow best on chocolate agar under 10 percent carbon dioxide.

Rarely, this organism has been associated with septicemia,[5] meningitis,[6] endocarditis,[7] otitis media[8] and conjunctivitis.[9] Recent reports of its recovery from transtracheal aspirates have implicated it in the pathogenesis of acute exacerbations of chronic bronchitis.[1] These reports have stressed the occurrence of such infections in patients with underlying chronic lung disease. Ninane and co-workers[1] have recovered *B catarrhalis* from 15 of 190 transtracheal aspirate specimens from retired coal miners with exacerbations of chronic bronchitis. Fourteen of their isolates were obtained in pure culture.

One case of acute empyema has been reported.[10] This involved a 74-year-old man with chronic lymphocytic leukemia whose empyema fluid specimen yielded a pure culture of *B catarrhalis*. After nine days of antibiotic therapy, sterile fluid was obtained by repeat thoracentesis. A 64-year-old man with advanced IgA myeloma suffered a rapidly fatal *B catarrhalis* pneumonia.[2] Recently, *B catarrhalis* has been implicated as a causal agent of pneumonia in six additional patients.[3,4] In only one of these, however, was the organism cultured from secretions obtained directly from the lower respiratory tract by transtracheal aspiration.

Four of our patients had underlying medical illnesses, including two who had chronic obstructive lung disease. In addition, one was predisposed to recurring pneumonia because of hypogammaglobulinemia. Another had systemic lupus erythematosus and was receiving prednisone. One patient was previously healthy; he had concurrent legionnaires' pneumonia. In previous reports, *B catarrhalis* has been recovered simultaneously with *H influenzae* and *Streptococcus pneumoniae* from transtracheal aspirates. Two of our patients were simultaneously infected with *H influenzae*.

We did not carry out β-lactamase testing on most strains. In fact, all of our patients responded to treatment with ampicillin or other β-lactam antibiotics. Acute bronchitis and pneumonia associated with β-lactamase-producing *B catarrhalis* has been noted to respond to cefuroxime carbamate,[1] tetracycline[4] and to a combination of amoxicillin and clavulanic acid.[11] Rapid β-lactamase testing should be done on all isolates while awaiting the results of susceptibility studies. In our clinical experience, ampicillin is effective for the treatment of pneumonia caused by susceptible strains.

Gram-negative diplococci are frequently seen in Gram-stained smears of expectorated material. Their presence may reflect contamination by saliva. However, the finding of large numbers of these organisms with morphology typical of *Neisseria* and associated with polymorphonuclear cells in a purulent sputum specimen is uncommon. Intracellular location of these organisms is even more suggestive. This encouraged us to confirm their presence in the lung by transtracheal aspiration. Nongonococcal and nonmeningococcal Gram-negative diplococci are often reported as "*Neisseria* species" by clinical laboratories. In view of the emerging body of evidence implicating *B catarrhalis* as a pulmonary pathogen, efforts should be made to identify it specifically in specimens from the lower respiratory tract.

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Cutaneous Malignant Melanoma in Hawaii – An Update

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In an examination of the descriptive epidemiology of cutaneous malignant melanoma in Hawaii for the period of 1960 through 1980, we identified 589 cases of invasive disease. On analysis, we found that the incidence of cutaneous malignant melanoma increased substantially among all age groups, both sexes and all anatomic sites in whites during the study period. In contrast, little change in incidence was found for nonwhites. Our findings are in agreement with the hypothesis that solar ultraviolet radiation is a causal factor for the occurrence of this condition among whites.

The incidence of cutaneous malignant melanoma has been increasing among white populations for at least the past three decades[1-7] and possibly longer.[8,9] Although the cause of this dramatic increase is not yet certain, many investigators believe that increasing exposure of the skin to solar ultraviolet radiation plays the predominant role.[2,5-10]

In an earlier review of cutaneous malignant melanoma in Hawaii,[7] we reported that the age-adjusted incidence tripled in whites of both sexes between 1960 and 1977. Since that report, it has increased to even greater levels, as detailed herein. This continued increase prompted us to undertake a second epidemiologic analysis of cutaneous malignant melanoma in Hawaii in hopes that further light might be shed on its cause.

Methods

All case information regarding malignant melanoma of the skin was derived from the statewide, population-based Hawaii Tumor Registry, in operation since 1960 and a member of the SEER (Surveillance, Epidemiology and End Results) Program of the National Cancer Institute since 1973. All resident cases of malignant melanoma originating in the skin and diagnosed from 1960 through 1980 were identified, along with the diagnosis date, age, sex and ethnicity of patients. The anatomic location of the primary tumor was also identified.

Population estimates used in the calculation of incidence rates were determined for 1960 through 1970 from the decennial census with linear interpolation for intercensal years. For 1971 through 1980, population estimates were those provided by Dr. Thomas Burch of the Hawaii State Department of Health and were based on that department's ongoing Health Surveillance Program, which samples 2 percent of Hawaii households each year. Where age-adjusted rates are shown, the World Standard Population was used.[11] Although a number of cases of in situ cutaneous malignant melanoma were diagnosed during the study period, only invasive cases were included in the rate calculations so as to avoid an apparent rate increase that might be due only to increased screening and biopsy. Unfortunately, consistent pathologic criteria could not be applied in defining in situ cases, as pathology slides were often not available. Instead, in situ cases were defined as those so specified in the pathology reports abstracted by the Hawaii Tumor Registry.

Results

During the study period of 1960 through 1980, there were 645 cases of cutaneous malignant melanoma diagnosed among Hawaii residents. Of these, 589 (91.3 percent) were invasive at the time of diagnosis and the analyses that follow will be restricted to these invasive cases.

In all, 473 cases (80.3 percent) were diagnosed in whites and 116 (19.7 percent) in nonwhites. In comparison, whites constituted only 34.2 percent of the

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Submitted, revised, July 2, 1982.

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TABLE 1.—*Invasive Cutaneous Malignant Melanoma Among Hawaii Residents, 1960 Through 1980*

Age at Diagnosis	Number of Cases			
	Whites		Nonwhites	
	Male	Female	Male	Female
0-19	4	4	2	4
20-29	35	37	4	7
30-39	48	43	5	13
40-49	51	35	7	5
50-59	58	29	18	6
60-69	54	26	16	7
70-79	26	14	11	4
80+	5	4	4	3
TOTALS	281	192	67	49

TABLE 2.—*Invasive Cutaneous Malignant Melanoma Among White Residents of Hawaii by Time Period of Diagnosis and Sex*

When Diagnosed Years	Number of Cases		
	Male	Female	Total
1960-1962	9	6	15
1963-1965	20	12	32
1966-1968	16	20	36
1969-1971	29	20	49
1972-1974	43	25	68
1975-1977	72	41	113
1978-1980	92	68	160
1960-1980	281	192	473

state's population in 1970. A further distribution of these cases by age, sex and ethnicity is shown in Table 1. As can be seen, a large proportion of cases of cutaneous malignant melanoma was diagnosed among persons younger than age 40 (28.2 percent for all male patients and 44.8 percent for all female patients).

The frequency of the diagnosis of melanoma of the skin among whites increased steadily during the study period as shown in Table 2. The dramatic increase in the incidence of this condition among whites is shown in Figure 1. There appears to be no indication that this incidence rate is not continuing to increase. In definite contrast, the cutaneous malignant melanoma incidence among nonwhites remained almost stable during the same period (broader time groupings were used in calculating average annual rates among nonwhites because the small number of cases resulted in rate instability). The very high incidence of cases of invasive melanoma of the skin observed among whites in Hawaii during 1978 through 1980 (24.0 per 100,000 in men and 19.5 per 100,000 in women) is among the highest reported in the world.[11]

As shown in Figures 2 and 3, the increase in incidence of cases of malignant melanoma over time is present among all age groups of whites. These data (plotted on semilog graphs) suggest no difference in the rate of increase among the age groups examined. It also can be noted in these figures that the incidence of cutaneous malignant melanoma among white men and women differs little up to age 54, but that rates in men are substantially higher for ages 55 and over.

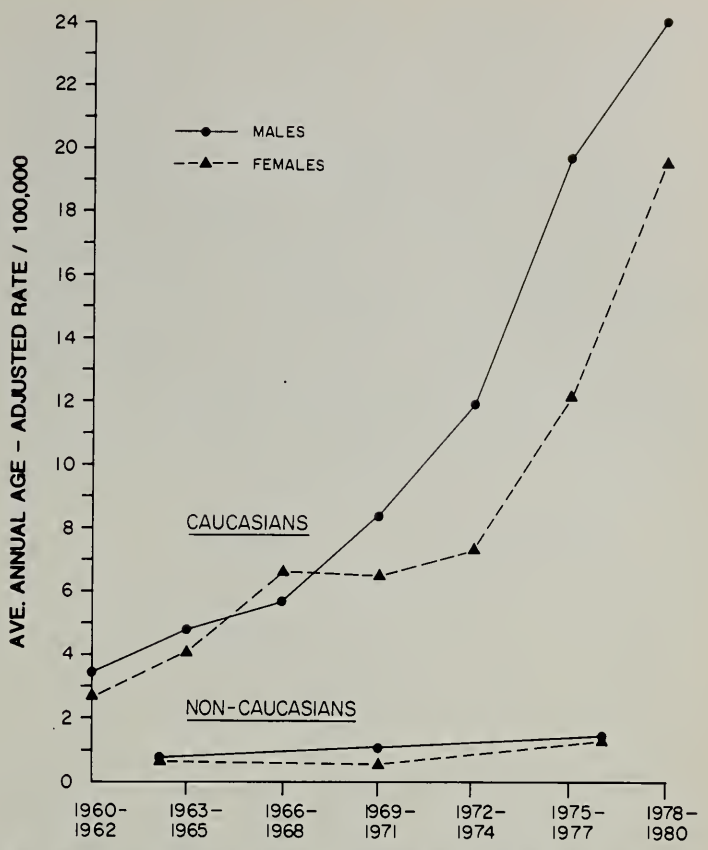

Figure 1.—Incidence rates of invasive cutaneous malignant melanoma among whites and nonwhites in Hawaii by sex and year of diagnosis, 1960 through 1980.

In Figures 4 and 5 the increase in cutaneous malignant melanoma incidence among whites is examined for various anatomic sites. The male/female differences in anatomic distribution of this condition are also apparent, with malignant melanoma of the skin of the head, neck and trunk more common in men and that of the lower extremities more common in women. A generally consistent increase in cutaneous malignant melanoma incidence for all four anatomic sites is seen for both sexes with the exception of that of the lower extremities. For this anatomic site, the incidence in men and women was curiously equal during 1972 through 1977, only to diverge in opposite directions in 1978 through 1980. Thus, cutaneous malignant melanoma of the lower extremities in men represents the only instance of decreasing rates in the most recent period.

The population in Hawaii consists of several ethnic groups, including Japanese (about 29 percent), Hawaiian/part-Hawaiian (about 18 percent), Filipino (about 11 percent), Chinese (about 5 percent) and others. As shown in Table 3, the average annual age-adjusted incidence of cutaneous malignant melanoma among these groups has not been very different during the study period. Moreover, each of these ethnic groups has shown only a tenth or less of the risk of malignant melanoma of the skin as that among whites. This risk differential by ethnicity has, of course, been increasing during the study period, as shown in Figure 1.

The effect of ethnicity on the risk of this condition

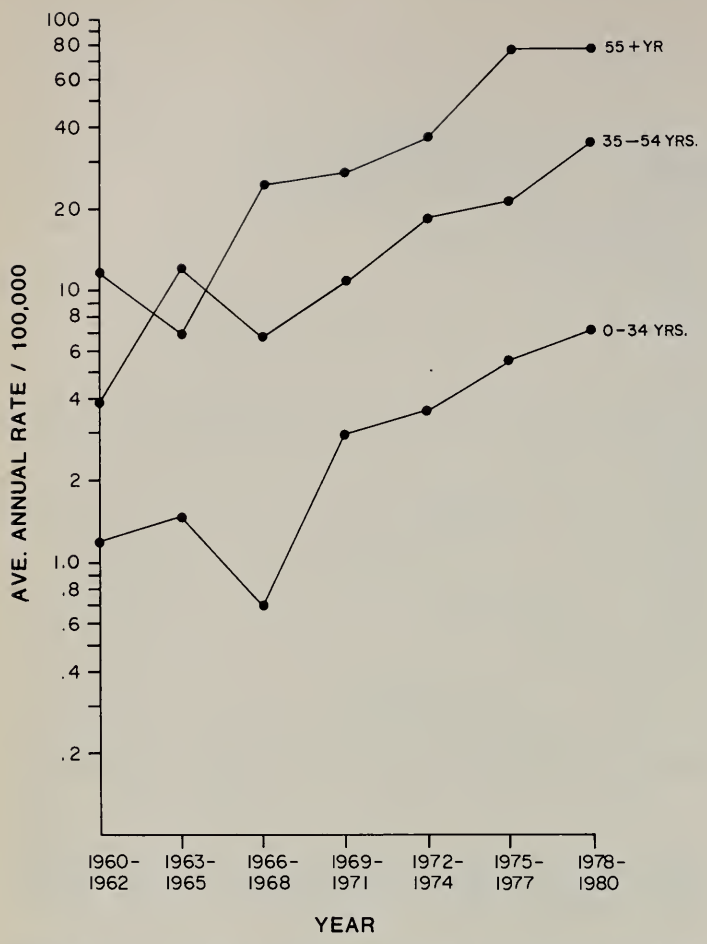

Figure 2.—Incidence of invasive cutaneous malignant melanoma by age among white men in Hawaii, 1960 through 1980.

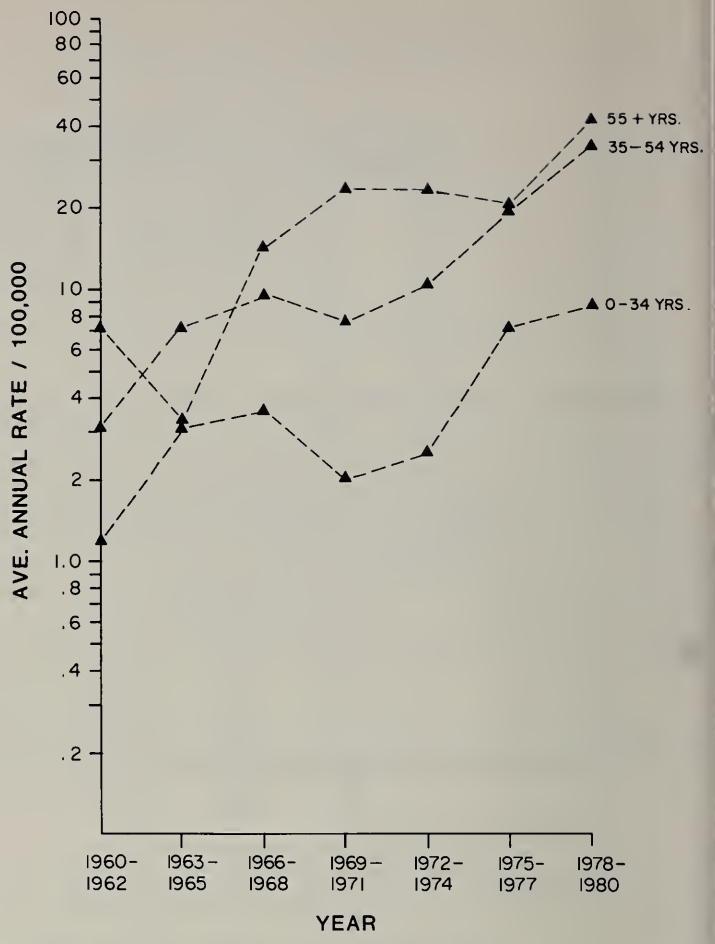

Figure 3.—Incidence of invasive cutaneous malignant melanoma by age among white women in Hawaii, 1960 through 1980.

developing is apparent in Hawaii even within the white group. About 10 percent of whites in Hawaii are of Portuguese ancestry as a result of large migrations of farm laborers from the Azores in the late 19th century. Exact population figures for the Portuguese population are not available, but cancer cases are coded for Portuguese ancestry by the Hawaii Tumor Registry, so that proportional cancer incidence during the study period could be estimated. Among Portuguese men, cutaneous malignant melanoma contributed only 0.5 percent of all cancer cases, and among Portuguese women, only 0.2 percent. In comparison, cutaneous malignant melanoma contributed 4.7 percent of all cancer cases among non-Portuguese white men and 3.1 percent among non-Portuguese white women.

Discussion

The outstanding observation of this report is the rapidly increasing incidence of cutaneous malignant melanoma among whites in Hawaii. This is a phenomenon that has consistently been reported among whites elsewhere in the United States,[8,9] Scandinavia,[1,2,4,9] England,[5] Israel[6] and Australia.[3] The worldwide nature of the phenomenon leaves no doubt of its validity. Incidence rates in tropical areas such as Hawaii and Queensland, Australia,[12] are high enough to make melanoma of the skin one of the more common forms of cancer.

In contrast to the rising rates of this malignancy among whites in Hawaii, there is little suggestion of increasing rates among nonwhites. Cutaneous malignant melanoma remains a very uncommon form of malignancy among all nonwhite groups in Hawaii.

If, as strongly suspected by many investigators, solar ultraviolet radiation plays the predominant role in causing malignant melanoma of the skin, then most of the descriptive epidemiology of the disease in Hawaii is understandable. The tropical location of Hawaii at 20°N latitude causes it to receive relatively high levels of solar ultraviolet radiation year-round.[13] Accordingly, whites in Hawaii would be expected to have high rates of cutaneous malignant melanoma, as indeed they do. The incidence of this condition would probably be even higher were it not that a substantial proportion of Hawaii's white population is apparently resistant to melanoma because of Portuguese ancestry.[14]

The increase in the incidence of cutaneous malignant melanoma among whites in Hawaii during the past two decades, which is noted among all age groups, in both sexes and in all anatomic locations, is consistent with general observations and knowledge about secular changes in clothing styles and recreational patterns. (The only exception to this trend, that noted in male lower extremities, may simply be an anomaly produced by small numbers—only five cases contribute to the

decreased rate in 1978 through 1980). The trend in Hawaii, as in most western countries, has clearly been toward more revealing clothing and beachwear and toward more leisure time spent in the sun. Sexual differences in clothing styles are reflected in the anatomic distribution of cutaneous malignant melanoma, with higher rates on the trunk for men (who often bare the complete trunk in contrast to women) and higher rates on the lower extremities of women. The higher rates of melanoma of the skin of the head and neck of men may reflect sexual differences in clothing styles (hats), hairstyles, hair loss, cosmetic use or outdoor work.[15]

The much lower melanoma incidence rate among all nonwhite groups almost certainly reflects the protection from solar radiation afforded these groups by their greater concentration of cutaneous melanin, which absorbs the ultraviolet energy before DNA damage occurs.

Widespread recognition of the probable causal association between solar radiation and cutaneous malignant melanoma by both health professionals and the general public is imperative if the alarming increase in the incidence of this malignancy is to be reversed. Recent investigations give reason to hope that such a reversal might be possible within a few years if solar exposure habits could be changed. An increased incidence of malignant melanoma has been shown to follow increased sunspot activity[8] and hours of sunshine,[5] with a lag time of two years or less. There is also evidence that a proportion of cases of cutaneous malignant melanoma may follow intense solar exposure by an even shorter period, as suggested by summertime peaks in diagnosis.[4,16,17]

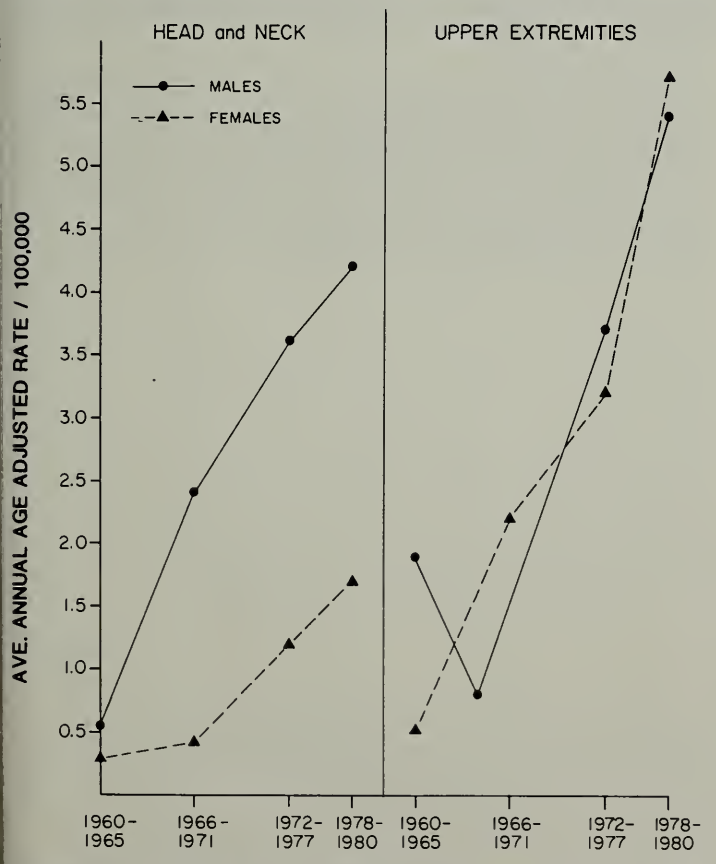

Figure 4.—Incidence of invasive cutaneous malignant melanoma of the head and neck and upper extremities among whites in Hawaii, 1960 through 1980.

Professional and administrative workers, clerks and salespersons have a higher incidence of cutaneous melanoma than manual and unskilled workers, suggesting that intermittent leisure-time exposure increases risk.[18] Support for this concept is also forthcoming from analysis of the occupational patterns of cutaneous malignant melanoma for different anatomic sites. Office work is associated with a large excess of melanoma of the trunk and limbs, whereas outdoor work is associated with an excess of melanoma on the skin of the head and neck.[15] A cohort analysis of 5,108 cases of cutane-

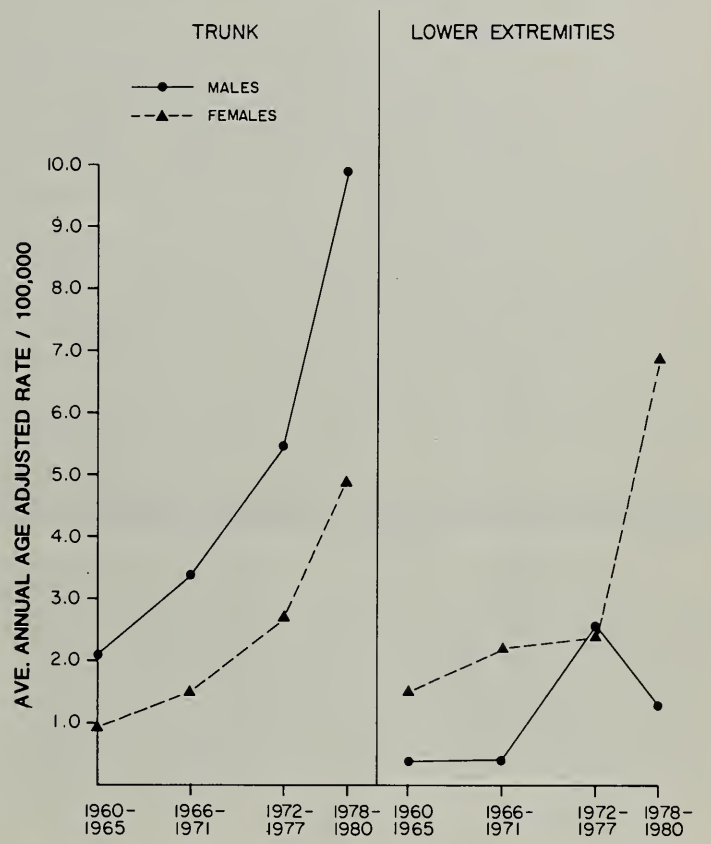

Figure 5.—Comparison of incidence of invasive cutaneous malignant melanoma of the trunk and lower extremities among whites in Hawaii, 1960 through 1980.

TABLE 3.—*Average Annual Age-Adjusted Incidence of Cutaneous Malignant Melanoma Among White and Nonwhite Ethnic Groups in Hawaii, 1960 Through 1980*

Ethnic Group	*Number of Cases**	*Rate in Both Sexes*
Whites	473	10.4 per 100,000†
Hawaiians/part-Hawaiians	22	1.1 per 100,000
Filipinos	15	0.9 per 100,000
Chinese	8	0.9 per 100,000
Japanese	35	0.7 per 100,000

*The remaining 36 cases in nonwhites either could not be assigned to a specific ethnic group because of racial admixture not involving Hawaiian stock, or belonged to one of the less-populous ethnic groups (Korean, Samoan, Vietnamese, black).

†In comparison, the same rate among whites living in areas of the United States covered by the Third National Cancer Survey in 1969 through 1971 was only 4.1 per 100,000.[20]

ous malignant melanoma in Norway has found a leveling off of age-specific incidence curves for the trunk and lower limbs at older ages within cohorts.[2] This could be explained by a lessened tendency with age to overexpose one's skin to the sun, resulting from experience, changed recreational habits or reduced peer pressure. This explanation would also suggest that changes in sun-exposure habits may affect the risk of cutaneous malignant melanoma developing rather rapidly.

Some experimental evidence suggests that exposure to ultraviolet light may increase the rate of melanoma growth either directly or indirectly.[10] Such an influence on the growth rates of latent melanoma cells might be an explanation for the association of cutaneous melanoma incidence with sunspot activity[8] and increased summer solar radiation.[4,16,17]

Given the body of evidence now available, there seems little reason to doubt that solar ultraviolet radiation exposure contributes significantly to the risk of cutaneous malignant melanoma in whites. However, there are notable inconsistencies in the evidence, in particular the anatomic distribution of lesions. Among white men in Hawaii, the incidence of melanoma is higher on the trunk than either the head and neck or upper extremities, though the trunk is certainly more often covered. Among white women, the incidence of cutaneous malignant melanoma is about equal for the trunk and upper extremities and much lower for the head and neck. Such observations might be explainable, however, if we possessed more knowledge of the role played by such factors as body hair, shaving and cosmetics in the risk resulting from solar exposure.

We also must not ignore the possible contribution of nonsolar factors to the risk of cutaneous malignant melanoma developing.[19] Genetic predisposition clearly plays a role, and dietary factors (particularly retinoids), trauma, hormonal factors, occupational exposures, viruses and certain drugs may also influence risk. However, it is difficult to imagine any hypothesis incorporating these nonsolar factors that could explain the astounding increase in cutaneous malignant melanoma incidence among whites during the past few decades, particularly in view of the lack of a similar increase among other ethnic groups. Accordingly, it seems probable that modification of solar exposure patterns is currently the most reasonable approach to reducing risk among whites.

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Coccidioidomycosis: Early Immunologic Findings

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T and B lymphocyte number and lymphocyte response to phytohemagglutinin, pokeweed mitogen, concanavalin A, coccidioidin and streptokinase-streptodornase (SKSD), plus monocyte ingestion of coccidioidin- and IgG-coated chicken erythrocytes were measured in 5 patients with coccidioidal meningitis, 11 with nonmeningeal extrapulmonary coccidioidomycosis and 5 with localized pulmonary infections. These cases were evaluated within six months of the onset of infection. Lymphocytic responses to phytohemagglutinin, pokeweed mitogen, concanavalin A, SKSD and coccidioidin and monocytic ingestion of coccidioidin- and IgG-coated chicken erythrocytes were severely decreased in patients with meningeal and nonmeningeal, extrapulmonary coccidioidomycosis but not in patients with localized pulmonary infections. T and B cell numbers, however, were normal in all groups. Thus, defects in cellular immunity are involved in the pathogenesis of extrapulmonary coccidioidomycosis and measurements of lymphocytic and monocytic function may identify patients prone to extrapulmonary infection.

The cellular immune response is a critical factor in the pathogenesis of coccidioidomycosis.[1,2] Several studies have shown that impairments in skin hypersensitivity and lymphocytic response to coccidioidin are common in patients with disseminated disease but not in those with less severe pulmonary infections.[3-5] Because patients in these studies had their infection for extended periods of time, information on the immune response in the early stages of coccidioidomycosis is limited. A unique opportunity to study this relationship occurred in 1978 when an epidemic of coccidioidomycosis followed a severe dust storm in the Sacramento Valley.[6] This report describes lymphocyte and monocyte function in 5 patients with coccidioidal meningitis, 11 with nonmeningeal extrapulmonary coccidioidomycosis and 5 with localized pulmonary infection, all of whom were infected for less than six months.

Methods

Patients

Clinical data for the patients in whom coccidioidomycosis developed following the dust storm of December 20 and 21, 1977, are summarized in Table 1. The five patients with meningitis had a positive culture of a biopsy specimen from a meningeal or nonmeningeal site and complement-fixing antibody in their cerebrospinal fluid. Cases diagnosed as disseminated nonmeningeal coccidioidomycosis had *Coccidioides immitis* in biopsy specimens or cultures from extrapulmonary sites. These patients were treated with amphotericin B or amphotericin B methyl ester. Patients with pulmonary coccidioidomycosis had roentgenographic evidence of infection and serum complement-fixing antibody. The pulmonary infection was self-limiting in four cases and persistent in one (No. 21).

Immunologic Studies

Immunologic tests for delayed hypersensitivity to coccidioidin, T and B lymphocyte and monocyte function and complement-fixing antibody to *C immitis* were carried out from two to six months following the onset of illness. Skin tests were done by intradermal inoculation of 0.1 ml of coccidioidin (Cutter Laboratories,

Refer to: Miller CH, MacKenzie MR, Paglieroni T, et al: Coccidioidomycosis: Early immunologic findings. West J Med 1983 Jan; 138:55-59.

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ABBREVIATIONS USED IN TEXT

E=sheep erythrocytes
SKSD=streptokinase-streptodornase

1:100). Indurations that were 0.5 cm or greater at 48 hours were recorded as positive.

Surface Markers

Venous blood was collected in syringes containing 20 units of preservative-free heparin per milliliter of blood. Monocytes were removed from these preparations by adherence to glass surfaces or by the ingestion of carbonyl iron.[7] The remaining mononuclear cells were separated on Ficoll-sodium metrizoate (Hypaque) gradients.[8] The number of sheep erythrocyte receptor-bearing cells (E), complement receptor-bearing cells and surface immunoglobulin-bearing cells was determined on monocyte-depleted cell populations by methods previously described.[9]

Lymphocyte Transformation Assays

Lymphocyte transformation was tested by incubation with mitogens and antigens. Gradient-isolated mononuclear cells (phagocytic cells were not removed) in RPMI 1640 were stimulated with 25 μg per culture of phytohemagglutinin and concanavalin A, 5 μl per culture of pokeweed mitogen, 50 μl of coccidioidin dilutions that ranged from 1:10 through 1:512 and 50 units per ml of streptokinase-streptodornase (SKSD). The coccidioidin was dialyzed extensively against saline before use. The SKSD was reconstituted from the lyophilized product in 0.01 mol per liter phosphate-buffered saline at a pH of 7.5 and stored at a concentration of 1,000 units per ml.[9]

Monocyte Function

The ability of freshly collected monocytes to ingest chicken erythrocytes that were coated with coccidioidin or human gamma globulin (IgG) was determined by the method of Huber and Fudenberg.[10] Antigen coating was achieved by incubating 10 ml of a washed 2 percent suspension of chicken erythrocytes for ten minutes with an equal volume of 0.05 mg per ml of tannic acid solution. Ten million tannic acid-treated chicken erythrocytes were reacted with 1.0 mg per ml of IgG, or 0.1 ml of the dialyzed coccidioidin solution. The appropriate coccidioidin dilution was determined by hemagglutination inhibition testing.[11] The antigen-coated chicken erythrocytes were washed in phosphate-buffered saline, centrifuged at 1,500 rpm and resuspended in 1 ml of phosphate-buffered saline. The presence of antigen on the erythrocyte surface was confirmed by hemagglutination testing. A suspension containing antigen-coated or control chicken erythrocytes in RPMI 1640 containing 10 percent fetal calf serum was added to 5×10^4 monocytes that had previously settled onto tissue culture chamber slides (Lab-Tek). The mixture was incubated for 60 minutes. After washing, the cells were fixed in 100 percent methanol and stained with a Wright's-Giemsa mixture; 200 monocytes were counted and the percentage of cells with two or more ingested chicken erythrocytes was recorded.

Results

Table 2 shows lymphocyte surface marker patterns in patients with coccidioidomycosis and in normal persons. The surface marker patterns of lymphocytes from patients with meningeal, nonmeningeal, disseminated and pulmonary infections were similar to those observed in persons whose skin test results were negative,

TABLE 1.—*Clinical Characteristics of Patients in Whom Coccidioidomycosis Developed Following the Dust Storm of December 20 and 21, 1977*

Case No.	Age	Sex	Race	Site of Infection	Skin Test Result	Complement Fixation Test	Response
1	26	♂	White	Meningeal	Neg	1:32	Died
2	50	♂	White	Meningeal	Neg	1:256	Died
3	53	♂	Black	Meningeal	Neg	1:64	Died
4	60	♂	White	Meningeal	Pos	1:32	Recovered
5	66	♂	Black	Meningeal	Neg	1:32	Died
6	21	♂	Black	Disseminated	Pos	1:256	Died
7	26	♂	Black	Disseminated	Pos	1:16	Recovered
8	29	♀	Black	Disseminated	...	1:256	Recovered
9	34	♂	Black	Disseminated	Neg	1:128	Recovered
10	36	♂	Black	Disseminated	Neg	1:256	Recovered
11	41	♂	Black	Disseminated	Neg	1:32	Died
12	43	♂	Black	Disseminated	...	1:16	Recovered
13	46	♂	Mex-Amer	Disseminated	Neg	1:16	Recovered
14	48	♂	Black	Disseminated	...	1:64	Recurrence
15	61	♂	Black	Disseminated	...	1:64	Died
16	77	♂	White	Disseminated	Pos	1:2	Recovered
17	24	♀	White	Pulmonary	Pos	1:4	Recovered
18	27	♂	Black	Pulmonary	Pos	1:64	Recovered
19	32	♀	Mex-Amer	Pulmonary	Pos	1:128	Recovered
20	42	♂	White	Pulmonary	Pos	1:256	Recovered
21	50	♀	Mex-Amer	Pulmonary	Pos	1:16	Persistence

except for the E rosette marker, which was significantly lower in disseminated disease.

Lymphocyte transformation responses following stimulation with mitogens and antigens are shown in Figures 1 and 2. Patients with meningeal and nonmeningeal disseminated coccidioidomycosis had similar and significantly reduced ($P<.05$) responses to phytohemagglutinin, pokeweed mitogen and concanavalin A when compared with responses of cells from normal persons or patients with pulmonary coccidioidomycosis (using Student's *t* test). Lymphocyte transformation was affected in the same manner in the studies that tested responses to coccidioidin and SKSD. That is, the lymphocytes of patients with meningeal and disseminated nonmeningeal coccidioidomycosis did not respond to coccidioidin and responded less well to SKSD than did the lymphocytes of patients with pulmonary infection, which showed fivefold increases in blastogenic response to coccidioidin ($P<.01$) and normal blastogenic responses to SKSD. No blastogenic response to coccidioidin occurred in patients with dermal hypersensitivity to coccidioidin or in those with anergy. No significant difference between patient groups and normal persons was noted in the unstimulated cultures.

TABLE 2.—*Lymphocyte Surface Markers in Patients With Coccidioidomycosis*

Diagnosis	Number of Patients	E Rosette Mean %	E Rosette SD	EAC Rosette Mean %	EAC Rosette SD	SIg Mean %	SIg SD
Normal	20	63	±8	16	±5	20	±5
Meningitis	5	50	±17	23	±10	31	±17
Disseminated	11	42	±13*	27	±12	31	±12
Pulmonary	5	61	±7	17	±7	17	±5

Abbreviations: E=sheep erythrocyte receptor-bearing cells, EAC=complement receptor-bearing cells, SIg=surface immunoglobulin-bearing cells, SD=standard deviation.

*$P<.01$ when compared with normal values.

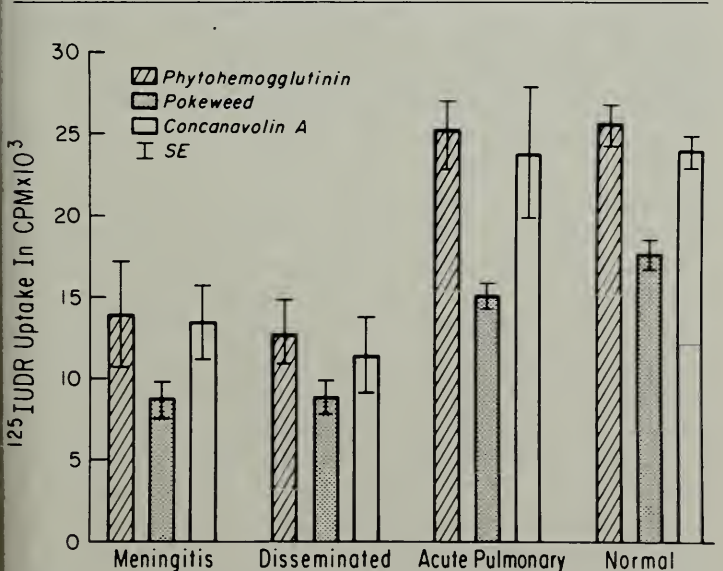

Figure 1.—Lymphocyte responses to mitogens in patients with different forms of coccidioidomycosis. CPM=counts per minute, ^{125}IUDR=iododeoxyuridine I 125, SE=standard error.

Findings from the experiments testing the ability of monocytes from patients with different forms of coccidioidomycosis to ingest coccidioidin- or IgG-coated chicken erythrocytes are depicted in Figures 3 and 4. In general, monocytes from patients with pulmonary coccidioidomycosis showed enhanced ingestive capacities for coccidioidin-coated chicken erythrocytes when compared with monocytes from patients with meningeal or disseminated nonmeningeal infections. Monocytes from the latter groups ingested coccidioidin-coated chicken erythrocytes at the same rate as that observed in monocytes from normal, presumably uninfected controls. The same pattern was observed when human IgG was used as the antigen, except that in these experiments monocytes from normal persons had the same high

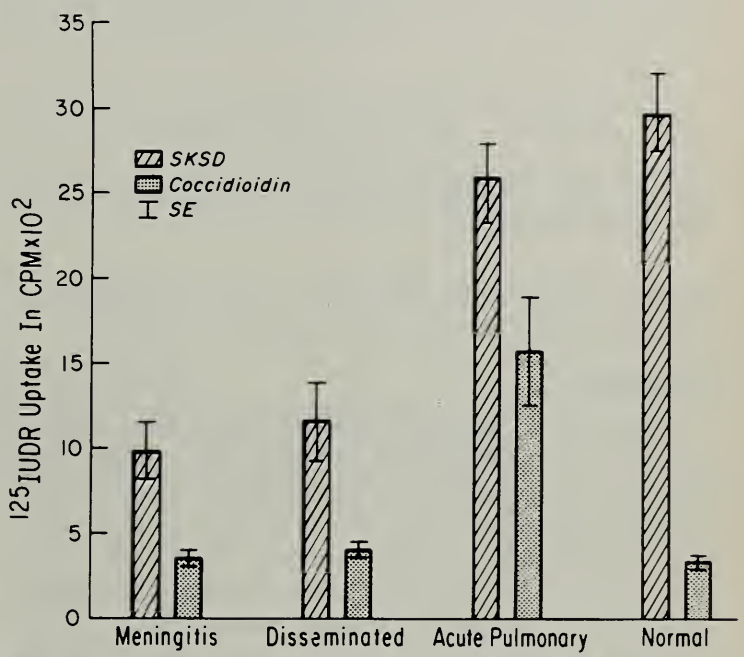

Figure 2.—Lymphocyte responses to antigens in patients with different forms of coccidioidomycosis. CPM=counts per minute, ^{125}IUDR=iododeoxyuridine I 125, SE=standard error.

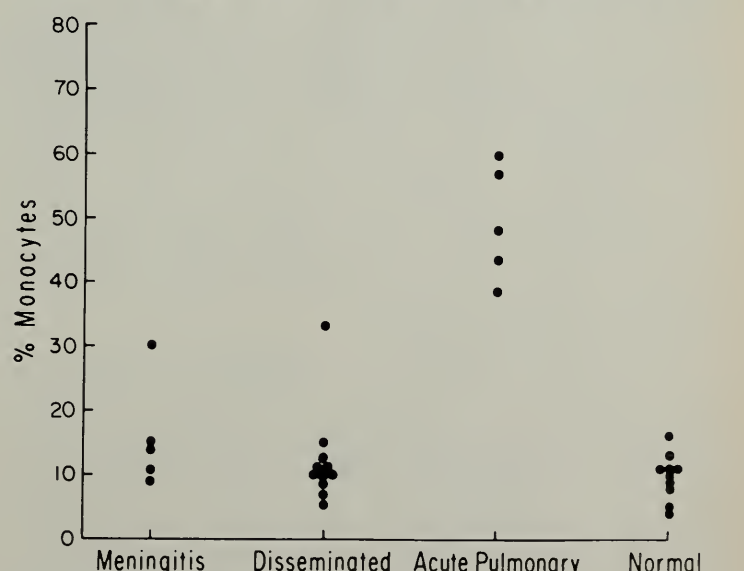

Figure 3.—Percentage of monocytes with two or more ingested coccidioidin-coated chicken erythrocytes in patients with coccidioidomycosis.

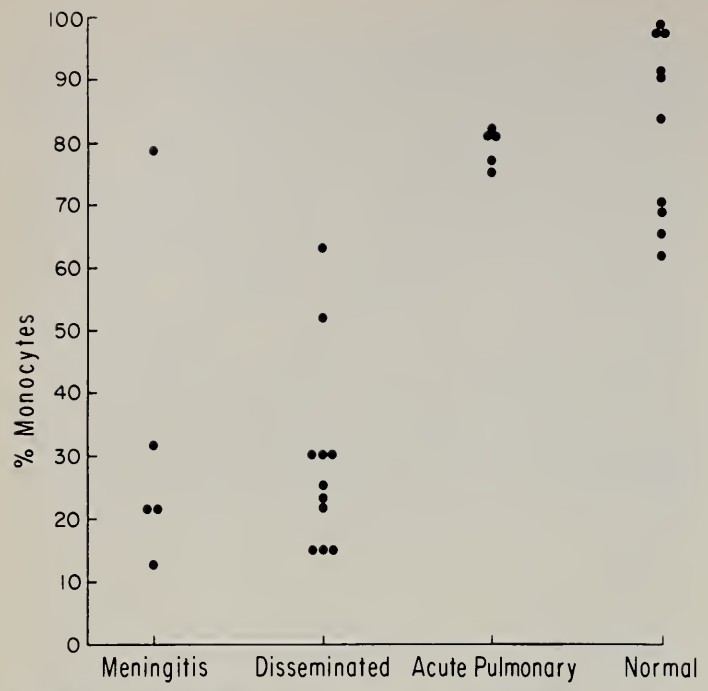

Figure 4.—Percentage of monocytes with two or more ingested human IgG-coated chicken erythrocytes in patients with coccidioidomycosis.

rates of erythrocyte ingestion as those observed in monocytes from patients with pulmonary diseases.

Discussion

These studies show that in the first months following infection, patients with meningeal and disseminated nonmeningeal coccidioidomycosis have impaired lymphocytic responses to mitogens and antigens and diminished monocytic capacity to ingest coccidioidin- and human IgG-coated chicken erythrocytes. The finding that lymphocytic transformation responses are reduced primarily in patients with extrapulmonary infection and that these reductions are most pronounced for coccidioidin accords with previous studies.[1,4,5] Because these patients were on amphotericin B or amphotericin B methyl ester at the time of study, it is possible that these agents may have contributed to the patients' reduced immunologic response. Because normal numbers of rosette-forming cells (T cells) were present in patients with meningitis, abnormality in T-cell function rather than number is probably responsible for the reduced immunologic response. The reduced immunologic response in patients with disseminated disease could be attributed to a reduced number of T cells as well as reduced functional capacity.

The reduced blastogenic lymphocyte response to coccidioidin did not always correlate with a lack of skin reactivity to the antigen. Four patients with extrapulmonary coccidioidomycosis had reduced lymphocyte blastogenic responsiveness and positive coccidioidin skin tests. This dissociation between skin and lymphocyte reactivity in patients with extrapulmonary disease has been noted by others and is unexplained.[3] Dermal reactivity occurred in the five patients with pulmonary infections, all of whom showed a blastogenic response to coccidioidin. This confirms previous reports that these two measurements of cell-mediated immunity usually agree in this form of the disease. Five of the eight patients with extrapulmonary infections and lack of delayed hypersensitivity response died compared with one death in the four patients who had dermal reactivity, suggesting that a positive delayed hypersensitivity test is associated with a more favorable clinical outcome.

The observation that monocytes from patients with extrapulmonary coccidioidomycosis have a defect in their ability to ingest coccidioidin- and IgG-coated chicken erythrocytes is a finding of significance. Mononuclear phagocytes are a major cellular defense against intracellular bacteria and fungi.[12-14] Studies in mice suggest that alveolar macrophages are important in the killing of *C immitis*.[15,16] Thus, the finding of an enhanced ingestive capacity for *C immitis*-coated chicken erythrocytes by monocytes from patients with pulmonary infections—but not those with more severe extrapulmonary disease—suggests that these monocytes would have similar differences in ingesting *C immitis* itself. That is, during the first months of infection patients whose monocytes are stimulated to ingest *C immitis* contain the infection within their lungs, whereas those whose monocytes fail to become activated are unable to halt the spread of infection. Because macrophages have an active role in both the afferent and efferent limbs of the immune response,[12,17] the phagocytic defect may either be responsible for or consequent to the T-cell impairment in blastogenic response to coccidioidin. Macrophages are involved in processing antigens for the T-cell response and an absence of this processing could account for the diminished T-cell response to coccidioidin. Alternatively, lymphokines from stimulated lymphocytes activate macrophages, increasing their phagocytic capacity, and a defect in this pathway may account for the impairment in ingestion. Regardless of the pathogenesis of the defect in monocyte function, the inability of monocytes from patients with extrapulmonary coccidioidomycosis to increase their ingestive capacity for coccidioidin-coated chicken erythrocytes is an important immunologic deficiency.

Our observations may aid clinicians faced with the dilemma of deciding the likelihood of extrapulmonary dissemination in a patient with a newly diagnosed coccidioidal infection. Detection of extrapulmonary lesions is critical in these patients because extrapulmonary infection warrants treatment with the highly toxic antifungal agent, amphotericin B, whereas localized pulmonary infection is usually self-limiting and need not be treated.[18] At present nuclear scanning with technetium Tc 99m methylene diphosphonate or gallium 67 is the most sensitive means for detecting extrapulmonary infection.[19,20] These procedures are recommended in patients in whom dissemination is suspected,[19,20] but because firm criteria for such suspicion do not exist, this important decision is often conjectural. Tests of immunologic function should help identify persons prone to dissemination, thereby improving the accuracy

of clinical judgments concerning the likelihood of extrapulmonary infection.

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Medical Practice Questions

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Assistant Surgeon for Laser Iridotomy

QUESTION:

Is it accepted medical practice to have an assistant surgeon present when a laser iridotomy is being done?

OPINION:

In the opinion of the advisory panel on ophthalmology, it is not necessary to have an assistant surgeon present when a laser iridotomy is done, except under special circumstances for selected patients such as those extremely ill.

Medical Progress

Plasmapheresis in Clinical Medicine

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Large-volume plasma exchange can now be rapidly and safely done using cell separator technology. Significant depletion of immunoglobulins and immune complexes can be achieved by repeated intensive plasmapheresis, but sustained depletion of these constituents requires concomitant immunosuppressive therapy. Plasmapheresis appears to work in some disorders by removing pathogenic antibodies, but other mechanisms of action have been postulated. It is the treatment of choice for thrombotic thrombocytopenic purpura and for the hyperviscosity syndrome due to macroglobulinemia. Apheresis can be useful in the treatment of many other disorders, most notably myasthenia gravis, glomerulonephritis associated with hemoptysis (Goodpasture's syndrome), refractory systemic lupus erythematosus, cryoglobulinemia and immune cytopenic disorders.

Plasmapheresis is a new and controversial modality in medicine. Most of the information on apheresis has been generated within the past five years, and the information that will definitively settle the role of plasmapheresis in medicine remains to be collected. There are two major controversies concerning plasmapheresis. First, strictly medically, to what extent does plasmapheresis actually ameliorate disease processes and to what extent are the results of a new technology being overenthusiastically received? The second issue is economic. Plasmapheresis is a very expensive form of treatment, often costing several thousands of dollars, and the therapeutic results must justify this cost. This review will briefly discuss the plasmapheresis procedure in general and its application to several selected disease entities and will conclude with a listing of current indications for plasmapheresis.

Description of Procedure

Plasmapheresis is a field of medicine that has been created by the availability of a new technology. Previously, small-scale plasma exchange was carried out by manual phlebotomy and centrifugation, but this process was slow and very cumbersome. Usually only 500 ml of plasma was removed, and to exchange more than a liter of plasma required a heroic and exhausting effort. The availability of the cell separator has dramatically changed this. Now 2 liters of plasma can be processed in an hour and 4 liters can be exchanged in two hours. Volumes of this magnitude could never be approached before.

Figure 1 shows a schematic of the plasmapheresis procedure as done on a continuous flow cell separator. Blood is removed from a patient and anticoagulated with a citrate solution. The blood then enters a centrifuge and is separated into cellular components and plasma. The cellular components are returned to the patient along with the replacement fluid of choice. The plasma can be harvested and collected.

How does large-volume plasma exchange affect plasma constituents? Plasma volume in humans is normally 40 ml per kg of body weight, or 2.5 to 3 liters in an average-sized person. By exchanging increasing numbers of plasma volumes, an intravascular marker will be depleted to an increasing extent (Table 1). A plasma exchange of 1.5 times the calculated plasma volume (usually an exchange volume of about 4 liters) will deplete an intravascular substance by about two thirds. Exchanging a larger volume gives a small additional yield. After exchanging 1.5 times the calculated plasma volume, different plasma constituents are affected differently.[1] Fibrinogen, the third component of complement (C3),

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ABBREVIATIONS USED IN TEXT

BSA = bovine serum albumin
GBM = glomerular basement membrane

and, when present, immune complexes are removed more efficiently than predicted, with a depletion of 75 percent to 85 percent. Immunoglobulins are removed as predicted, with a 65 percent depletion. Electrolytes, uric acid and selected proteins such as factor VIII are removed very inefficiently. With a properly carried out procedure, erythrocyte loss should be in the range of 30 ml. The platelet count will often be modestly reduced but thrombocytopenia to levels less than 50,000 per μl occurs in only 10 percent of cases. Following a single 1.5 times plasma volume exchange, these plasma constituents will recover at differing rates. Fibrinogen and C3 recover slowly, reaching their preexchange values in three to four days. Platelets recover to their previous level in one to two days and the coagulation factors, with the exception of fibrinogen, return to baseline values within hours. Recovery patterns for the immunoglobulins are more complex. IgG recovers to 40 percent towards the baseline within the first 48 hours, reflecting reequilibration from extravascular sources. Following this, recovery occurs at a slower pace with about 80 percent recovery at two weeks.

Potential Complications

Plasmapheresis is generally a well-tolerated and comfortable procedure. When compared with dialysis, it is much better accepted. There are many potential complications, however (Table 2). While the procedure is being carried out, patients may have chills that are usually related to the administration of large volumes of fluid cooler than body temperature. This can largely be obviated by the use of blood warmers. Citrate toxicity is common and is usually characterized by paresthesias, dizziness and headaches. This should respond promptly to intravenous administration of calcium. Hypotension can be the result of vagal reactions or of transient fluid depletion, and usually responds promptly to administration of fluid. When fresh frozen plasma is used as the replacement fluid, there is a risk of hypersensitivity reactions and of transmitting hepatitis. One recently recognized potential complication of the procedure is that drug concentrations may be substantially altered. At present there is little information as to how plasmapheresis affects the pharmacokinetics of specific drugs.

Most of the patient discomfort related to the plasmapheresis procedure is due to the need for vascular access. When possible, peripheral veins are used for such access. An 18-gauge needle is suitable for a return line, but a 14-gauge catheter is needed for the bleed line. When peripheral veins are not suitable, Scribner shunts or dialysis catheters must be used and one must then contend with the risks of placement and the thrombotic and infectious complications of these devices.

The depletion of fibrinogen and other coagulation proteins and platelets in a patient who is transiently anticoagulated might be expected to lead to a risk of bleeding complications. In fact, bleeding complications are rarely seen and some have raised the possibility that thrombotic complications related to depletion of antithrombin III might be more of a problem. Similarly, though one might expect that depletion of immunoglobulins and complement components may lead to a risk of infection because of the depletion of important opsonins, an increased risk of infections has not been an important problem. Only one report of a small group of patients treated for rapidly progressive glomerulonephritis has indicated a risk of opportunistic infection.[2]

Despite the long list of potential complications, plas-

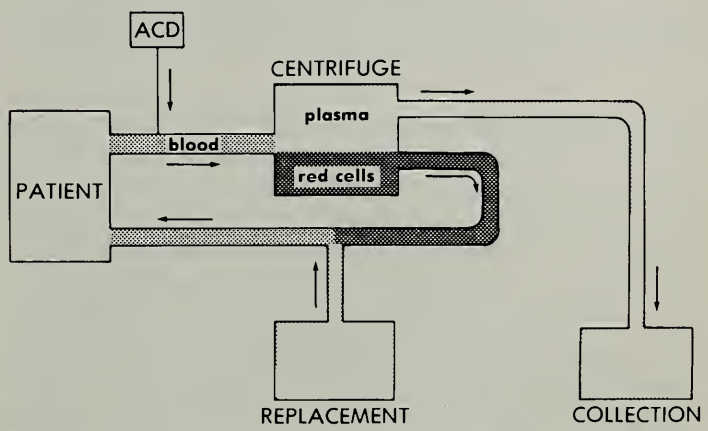

Figure 1.—Schematic of the plasmapheresis procedure. ACD = anticoagulant citrate dextrose solution.

TABLE 1.—*Relationship of Plasma Exchange Volume and Removal of Intravascular Substance*

Plasma Volume = 40 ml/kg		
No. Plasma Volumes	*Volume (ml)*	*Percent Remaining*
0.5	1,400	65
1.0	2,800	45
1.5	4,200	35
2.0	5,600	30

TABLE 2.—*Complications of Plasmapheresis*

- Related to procedure
  - Chills
  - Citrate toxicity
  - Hypotension
  - Hypersensitivity to fresh frozen plasma
  - Hepatitis from fresh frozen plasma
  - Changes in drug concentrations
- Access
  - Peripheral vein
  - Scribner shunt
  - Dialysis catheters
- Depletion of plasma constituents
  - Fibrinogen
  - C3
  - Immunoglobulins
  - ? Bleeding or thrombosis
- Mistakes
- Cost
- Unknown

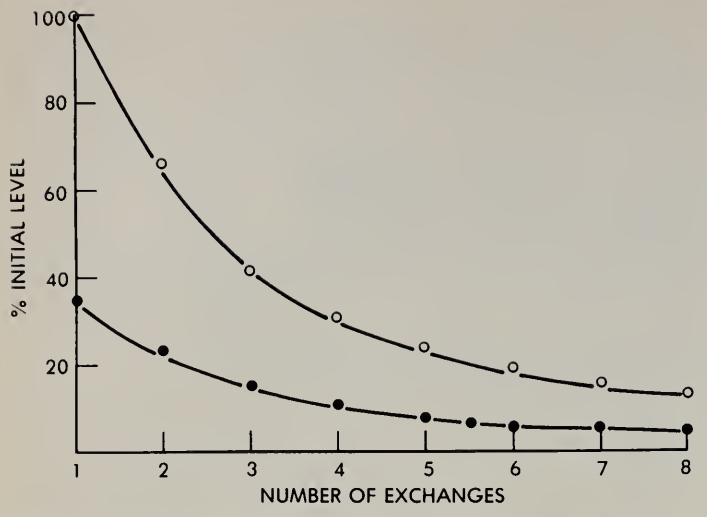

Figure 2.—Model of reduction in IgG with daily large volume plasma exchange. o--o preexchange, •--• postexchange.

mapheresis has proved to be a well-tolerated and safe procedure. At the University of California during the past four years, we have done more than 300 plasmapheresis procedures and have had only one significant complication. This was a myocardial infarction that occurred in an elderly woman with cryoglobulinemia. She made an uneventful recovery. However, this excellent safety record both at our center and at large apheresis centers may be due in part to the care with which the procedure is carried out and the close supervision used. Apheresis in our institution is done by a small group of well-trained nurses, and all procedures are closely supervised by a physician knowledgeable in apheresis and immediately available on the premises. If apheresis procedures become more widespread and are carried out in a less careful fashion, the complications rate may increase substantially. One of the important complications of plasmapheresis is its cost. At the University of California, our average cost per procedure is about $1,000. Since a "course" of plasmapheresis may involve repeated procedures, the cost may range from several thousand to as much as $15,000. Finally, we must recognize that apheresis is a new field and that other complications may become apparent in the future. The profound changes in plasma constituents that are caused by intensive apheresis may lead to consequences that we do not anticipate at this time.

The Role of Plasmapheresis in Immunologic Disorders

Many of the diseases for which plasmapheresis is advocated are thought to have an immunologic basis, and apheresis is often thought to work by removing a specific immunoglobulin G. One important question is how plasmapheresis would be expected to affect IgG levels. Total body IgG stores are about 1 gram per kg, or 70 grams in an average-sized man. About 52 percent of this is intravascular and available for depletion by apheresis. If one calculates the amount of IgG removed by apheresis and the amounts of net synthesis and catabolism, one can arrive at a model of how IgG levels would be expected to decline with repeated procedures. One must look at both the postexchange and preexchange values because immediate postexchange values are misleadingly low before reequilibration. With exchanges of 1.5 times the calculated plasma volume, the preexchange IgG level will fall below 30 percent of the baseline before a fifth procedure (Figure 2). This preexchange value will then reach a plateau of about 18 percent of the baseline value, which will reflect the point at which the synthesis rate is equal to the rate of removal.

Such models are inaccurate because many of the assumptions on which they are based are false. Probably the most important variable is the synthesis rate. It has been suggested that the body has homeostatic mechanisms that will lead to a compensatory increase in synthesis of immunoglobulin following depletion. There is a great deal of evidence for such an assertion. Researchers working with immunized laboratory animals have known for years that an animal often maintains a high titer of antibody despite repeated bleedings that might be expected to deplete a significant portion of its plasma volume. This question has been addressed in a more controlled way in laboratory studies in which rabbits were immunized to bovine serum albumin (BSA) and to a second antigen.[3] The anti-BSA antibodies were then selectively depleted by adsorption of plasma on BSA immobilized on a cellulose matrix. Significant depletion of the antibody was reported. Following such depletion, the anti-BSA antibody rebounded to 1.5 times the initial titer. There was no change in the titer of the antibody that was not affected by the adsorption procedure and there was no rebound seen after selective depletion of anti-BSA when this antibody was passively given. These experiments were extended the following year.[4] Rabbits were immunized either to bovine serum albumin or to BSA plus a second antigen. The singly immunized animals served as donors in exchange transfusion into the doubly immunized animals, leading to selective depletion of only one antibody. As before, the depleted antibody rebounded to two times the preexchange baseline. The antibody not depleted did not rebound.

How would an increased synthetic rate change the model calculations of IgG depletion? If daily large volume exchange were carried out and the synthetic rate merely doubled, the rate of depletion would be less steep and the plateau would be at 23 percent of baseline. The effect of increased synthesis is seen more dramatically in examining less intensive apheresis (Figure 3). With twice a week exchange, the IgG levels would fall to 40 percent of baseline. If synthesis merely doubled, IgG depletion would be minimal and preexchange would remain at 75 percent of baseline.

Once the problem of rebound antibody synthesis was recognized, attempts were made to abrogate the antibody response with immunosuppressive agents. The best explored regimen has been that of cyclophosphamide. In one study, mice were immunized to keyhole-limpet hemocyanin and a second antigen, and the singly

immunized animals were used as donors into the doubly immunized mice, leading to selective depletion of one antibody.[5] Once again the depleted antibody rebounded, this time to 1.8 times the baseline value. When a single large dose of cyclophosphamide (200 mg per kg) was given 24 hours after exchange, the titer rose to only 0.9 times the initial value. Another group alloimmunized dogs to bovine serum albumin and depleted the plasma of anti-BSA antibodies by adsorption over BSA immobilized on a charcoal matrix.[6] Following depletion, there was rapid return to the baseline. Cyclophosphamide in combination with cytosine arabinoside (but not cyclophosphamide alone) blunted this return to baseline values.

Several variables hamper the ability to predict changes in specific IgG values following plasma exchange. The inherent synthetic rates in people may vary widely, and it is known that patients with immunologically mediated diseases often have high synthetic rates. Whether the rebound in antibody synthesis seen in laboratory animals occurs in humans, and whether the results with alloantibodies can be applied to autoantibodies remain to be seen. To what extent cytotoxic agents and corticosteroids can blunt such a rebound in antibody synthesis in humans also is largely unknown. This effect may depend importantly on the dose used and duration of therapy. Furthermore, even if we know that a specific disease is caused by a specific autoantibody, we have no information on what amount of reduction in plasma titer is necessary to result in a clinical effect. One can only say in summary that in order to get significant depletion of an autoantibody, one would have to do frequent large volume exchange and take some measures to blunt a rebound increase in antibody synthesis (if such should occur).

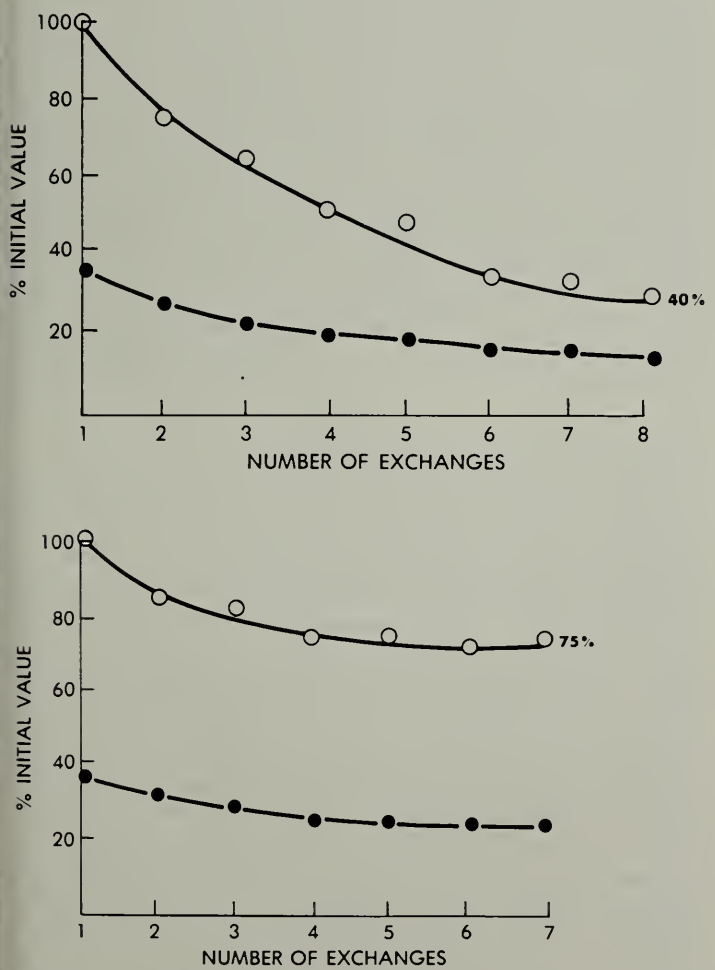

Figure 3.—Upper, Model of reduction in serum IgG level with twice a week plasma exchange. **Lower,** Model of reduction in serum IgG with twice a week plasma exchange (double synthetic rate). o--o preexchange, •--• postexchange.

Thrombotic Thrombocytopenic Purpura

Turning to specific disease entities, one of the most dramatic uses of plasmapheresis is in the treatment of thrombotic thrombocytopenic purpura. How plasmapheresis works in this disorder is unknown. If one believes that thrombotic thrombocytopenic purpura is caused by a circulating antibody that is cytotoxic to endothelial cells, then perhaps plasmapheresis works by depleting this antibody. If one believes that this disorder is caused by the absence of plasma factors, either of a normal inhibitor of platelet aggregation or of factors important in prostacyclin metabolism, then perhaps plasmapheresis merely enables one to infuse large amounts of fresh frozen plasma.

Although the mechanism of action of apheresis in treating thrombotic thrombocytopenic purpura is unknown, it is clearly effective. In 1976 exchange transfusion was reported to be a successful treatment for this condition.[7] Of 14 patients treated, 7 recovered, representing a great improvement of this center's previous greater than 90 percent mortality. Impressively, four patients showed dramatic resolution of neurologic deficits within hours of the exchange procedure, either awakening from coma or resolving dense paresis. Other groups confirmed these results. The following year when plasmapheresis was used instead of exchange transfusion, both patients who were so treated recovered, and the same dramatic and rapid neurologic improvement was again seen.[8] In reviewing the literature, I have found 69 reported cases of thrombotic thrombocytopenic purpura treated with plasmapheresis, with a 74 percent response rate. Our results over the past three years with four of five patients responding to plasma exchange are consistent with these reports.

Because we do not know how apheresis works in thrombotic thrombocytopenic purpura, one cannot write a specific prescription for a course of plasmapheresis. I would empirically recommend that large volume (1.5 to 2 times the calculated plasma value) be exchanged daily until all evidence of disease activity subsides. One should correct neurologic abnormalities and see a rise in the platelet count and the cessation of hemolysis as indicated by the normalization of the serum lactic dehydrogenase level and the rise in hematocrit value. Microangiopathic abnormalities may be seen on a peripheral blood smear for long periods despite the cessation of "active disease." Whether steroids or antiplatelet agents are useful in an adjunctive role will be answered only by controlled trials. Although plasmapheresis is the treatment of choice for

thrombotic thrombocytopenic purpura, one must keep in mind that it is a heterogeneous disease syndrome and not every patient will respond to plasmapheresis. If no response at all to therapy is seen within the first 48 to 72 hours, one should then seriously consider second-line therapies. The combination of splenectomy and the administration of steroids and dextran has led to impressive results in some patients, and the use of vincristine sulfate has recently been reported to be effective.

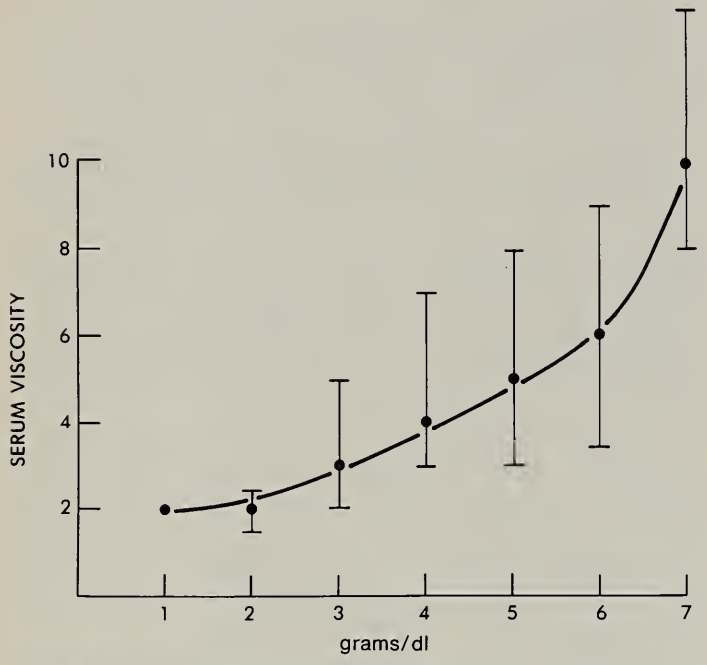

Figure 4.—Relationship of serum IgM concentration (•) to serum viscosity (indicated by vertical bar).

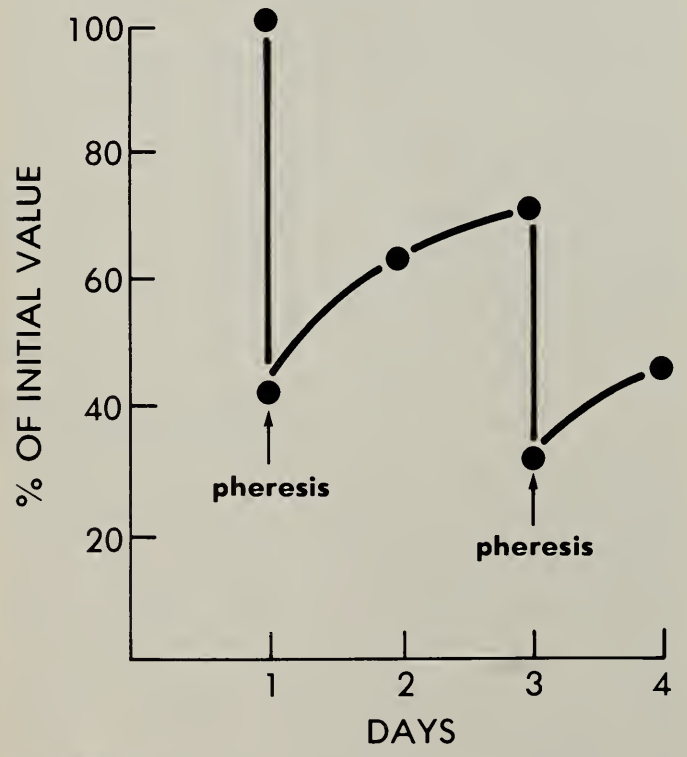

Figure 5.—Reduction in serum IgM concentration (•) by plasma exchange.

Waldenström's Macroglobulinemia

Another disease for which plasmapheresis is dramatically effective is the hyperviscosity syndrome. As serum IgM concentration rises about 6 grams per dl, serum viscosity increases dramatically (Figure 4). One would expect that a relatively small decrease in IgM concentration would lead to an important reduction in viscosity, and it is viscosity that causes the clinical syndrome. In a patient with Waldenström's macroglobulinemia whom we have repeatedly plasmapheresed, we have seen an acute reduction in IgM concentration to 40 percent of baseline after a single procedure, and an overall 50 percent reduction in serum concentration after equilibration following two large exchanges carried out two days apart (Figure 5). In general, one should expect the serum IgM concentration to decrease 60 percent (50 percent to 80 percent) by a single exchange of 1.5 times the calculated plasma volume. This should reduce the serum viscosity to below the symptomatic level.

In addition to its use in emergent treatment of hyperviscosity, plasmapheresis may be useful in the ongoing treatment of Waldenström's macroglobulinemia in the elderly group of patients who are poor candidates for chemotherapy. Because IgM is about 75 percent intravascular, its depletion is efficient. Patients often have a "threshold" level of plasma viscosity at which they repeatedly become symptomatic and one can then aim to maintain their viscosity below this level. It has been observed that patients can be repeatedly plasmapheresed for periods as long as two years without accelerating their requirement for plasmapheresis, suggesting that there was no compensatory increase in protein synthesis. On the average, patients with macroglobulinemia will require apheresis every two months, but some will require apheresis as infrequently as every four months. In these situations, plasmapheresis as the sole form of therapy may be a reasonable alternative to chemotherapy.

Immune Cytopenic Disorders

Plasmapheresis has been advocated for the treatment of a number of immunologically mediated hematologic disorders. One of the prototypes of a disease caused by a specific autoantibody is idiopathic thrombocytopenic purpura. The first report of a case of this disorder being successfully treated by plasmapheresis was flawed because vincristine was given several days before the procedure and could have been responsible for the "response."[9] Sporadic case reports have appeared but only one large series concerning plasmapheresis for idiopathic thrombocytopenic purpura has been reported.[10] In this study, five of nine acute cases of this disorder responded, and all five of these patients had sustained responses (in one case, requiring a second course of apheresis) and avoided the need for splenectomy. No responses were seen in the chronic cases. I find it difficult to understand why therapy was so successful for the patients with acute condition, since only one plasma volume was exchanged every two weeks. One

would not anticipate that this would lead to more than a 10 percent reduction in antibody titer and how this would lead to an important clinical effect is unclear. At the University of California, San Francisco, we have done apheresis in two patients with refractory idiopathic thrombocytopenic purpura who had failed therapy with high doses of prednisone, splenectomy, procedure and administration of vincristine and who were seriously bleeding and unresponsive to platelet transfusions. One of these two patients responded dramatically to plasmapheresis.

Plasmapheresis has been reported to be useful for other immune cytopenic disorders. Nine cases of autoimmune hemolytic anemia have been reported in the literature with response to apheresis in eight. Pure erythrocyte aplasia, which in many instances is due to an IgG autoantibody against erythroblasts, has been reported to respond to apheresis in three cases, two in patients with systemic lupus erythematosus. In the case unassociated with lupus, serial assays for the antibody tested in an in vitro system for erythroid progenitor cells showed progressive depletion of this antibody.[11] After the fifth large-volume plasma exchange antibody, the inhibitory activity was no longer detectable. Finally, some cases of aplastic anemia are associated with a serum IgG inhibitor of in vitro marrow growth. Most of these cases have been associated with systemic lupus erythematosus and two of three reported cases appear to have responded to a combination of plasmapheresis and immunosuppressive therapy.[12] In general, plasmapheresis will have a small role to play in the treatment of immune cytopenic disorders. Although it is effective in certain well-documented circumstances, plasmapheresis should be reserved for patients who are seriously ill and who have failed to respond with conventional therapy. It will hence be applied to a very small fraction of patients with these disorders.

Rheumatic Disorders

Systemic Lupus Erythematosus

Turning now from hematology to the rheumatic disorders, I would like to discuss the use of plasmapheresis in the treatment of systemic lupus erythematosus and to review some additional concepts of how plasmapheresis may work. In 1976 the results of plasmapheresis as treatment for eight patients with lupus were reported.[13] Four responded and the four responders were the same patients who had circulating immune complexes. The authors noted that immune complex levels fell more quickly than could be accounted for by the amount that had been directly removed by plasmapheresis. They postulated that some endogenous clearance mechanism for immune complexes had been activated. This hypothesis was supported by studies of reticuloendothelial function based on Fc receptor-mediated clearance of immunoglobulin-coated erythrocytes.[14] The clearance time of these erythrocytes was abnormal in 13 of 15 patients with lupus, and the degree of impairment of reticuloendothelial function appeared to correlate both with disease activity and with immune complex titer. Further studies showed an effect of plasmapheresis on reticuloendothelial function.[15] Ten patients with nephritis or vasculitis, several of whom had lupus, were studied using clearance of either immunoglobulin-coated or heat-damaged erythrocytes as an assay of reticuloendothelial function. For the patients studied with IgG-coated erythrocytes, all six patients had abnormal clearance times before plasmapheresis, and five of six had this abnormality completely corrected following a course of apheresis.

These studies support the hypothesis that in systemic lupus erythematosus, disease activity is related in some way to levels of circulating immune complexes. Large amounts of immune complexes may overload the clearance mechanisms of the reticuloendothelial system, leading to higher circulating levels of complexes and perpetuating the disease process in a vicious cycle. By reducing the level of immune complexes, plasmapheresis may allow the endogenous clearance mechanism to become active again, breaking the vicious cyle and leading to amelioration of the disease process. This concept remains a hypothesis, though there is experimental evidence to support it. The weakest link is in establishing a direct relationship between immune complex levels and disease activity.

Further clinical studies on the use of plasmapheresis for the treatment of systemic lupus erythematosus discussed the treatment of two patients with mild disease who received no medications.[16] Only a transient clinical response was seen, there was a very poor reduction in titers of anti-DNA antibodies and there was only a transient reduction in immune complex levels, which was followed by a rapid rebound to above the baseline value. The authors concluded that apheresis should not be used for these mildly ill patients and should not be used in the absence of steroid administration. Others have confirmed these results and have indicated that for mildly ill patients, plasmapheresis is not helpful and may be harmful. In this report, six more seriously ill patients who were receiving prednisone and cytotoxic agents were studied, and three of the six responded. There appeared to be a correlation between clinical response and reduction in anti-DNA antibody titers, with responders having a greater than 90 percent reduction and nonresponders having less than a 40 percent reduction in titer. Similarly, with respect to reduction in immune complex levels, responders had durable responses, but those who failed to respond had only a transient lowering of these levels.

One additional concept of how plasmapheresis might be effective in lupus was generated in a report of a gravely ill patient who had progressive disease despite maximal conventional therapy and who responded dramatically to plasmapheresis.[17] The patient's plasma before apheresis contained an activity that would inhibit suppressor T-cell function assayed against IgG synthesis in vitro, or against T-cell blastogenesis. Following successful therapy with plasmapheresis, this activity was no longer present. The authors speculated that plasmapheresis

may be effective because of the removal of an antisuppressor cell activity.

There is a great deal of experimental evidence that supports the notion of T-cell suppressor defects in patients with lupus. In New Zealand black and white mice (genetically bred so that lupus will develop), antilymphocyte antibodies appear before the development of overt disease and appear to increase before clinically recognizable disease appears. In patients with lupus, defects in T-cell suppressor activity have been reported. The deficiency appears to be due to a serum factor, since patients' serum will inhibit normal T-cell function. One explanation for this activity may be the finding of antibodies directed against the OKT8 antigen, which is present on the cytotoxic/suppressor subset of T lymphocytes. One report has correlated the presence of such anti-OKT8 antibodies with disease activity.[18] In this study, 12 of 14 patients with active disease had the antibody, whereas none of 15 patients with inactive disease did.

In summary, regarding the usefulness of plasmapheresis for patients with lupus, occasionally dramatic responses have been seen in patients who were failing despite maximal conventional therapy. Responses have been seen in a broad spectrum of disease manifestations, including those of central nervous system and of renal, pulmonary, hematologic and dermatologic systems. In reviewing the literature, I have found 47 reported cases with a 70 percent response rate. When only series with more than two patients are counted, the response rate drops to 50 percent (10 of 20). The mechanism of action of apheresis remains speculative. It is possible that anti-DNA antibodies, anti-T-cell suppressor antibodies or antibodies against hematologic progenitor cells are removed. Alternatively, immune complexes may be removed with consequent improvement in reticuloendothelial system function. However, these remain hypotheses and it is possible that apheresis works by currently unknown means.

Cryoglobulinemia

Another disease for which apheresis is occasionally useful is essential cryoglobulinemia. In 1980 five cases of cryoglobulinemia were reported and all responded to apheresis.[19] In 1981 five additional cases were reported, all five patients having serious disease manifestations despite treatment with prednisone and chlorambucil.[20] All patients responded to plasmapheresis enough to lower the mean cryocrit from 12 percent to 2 percent. The authors were particularly impressed with the improvement in renal function. Proteinuria was reduced from a mean of 6 grams to 1 gram a day, and creatinine clearance improved from a mean of 43 ml per minute to 67 ml per minute. In a separate study of Fc receptor-mediated clearance of IgG-coated erythrocytes in patients with cryoglobulinemia, it has been observed that it is that subset of patients with glomerulonephritis that have impaired clearance times.[21] Perhaps this finding is related to the improvement in renal function following apheresis. Cryoglobulinemia is an attractive disease to treat with plasmapheresis because the immune complexes that constitute the cryoglobulin are located largely intravascularly, and because the rate of synthesis (except in cases associated with myeloma) appears to be slow. Plasmapheresis can be recommended for such patients when they have significant disease activity despite conventional therapy.

Rheumatoid Arthritis

One disease for which plasmapheresis is not useful is rheumatoid arthritis. In 1979 it was reported that lymphocyte depletion would lead to improvement in disease activity.[22,23] Lymphocytes were depleted either by repeated thoracic duct drainage or lymphopheresis using the cell separator. In these uncontrolled reports, all of the six patients treated responded and responses were maintained for three to five months. In 1980 plasmapheresis was reported to be useful in the treatment of rheumatoid arthritis.[24] Patients were apheresed moderately intensively, with 21 plasma volumes exchanged during an 11-week period. Lymphocytes were also removed in 9 of these 20 patients. The authors reported that 18 of 20 patients responded and that responses were maintained for an average of four months. This report has been criticized on several grounds. First, the authors appeared overly enthusiastic in using the term "remission" to describe what were actually moderate responses. More important, the issue of the contribution of placebo effect could not be answered by this study. The same year, a controlled study of plasmapheresis in the treatment of rheumatoid arthritis was reported.[25] Patients were admitted to hospital and placed on a program of rest and physical therapy. In addition to this program of conservative care, patients were randomly selected to receive apheresis or not, with ten patients in each group. No differences in clinical outcome were seen between these groups, and these authors concluded that the benefit previously ascribed to plasmapheresis was actually a placebo effect. This study has several flaws, though. The amount of plasmapheresis—four plasma volumes exchanged over three weeks—was probably inadequate, and few of the patients were receiving prednisone or cytotoxic agents.

In 1981 the group at the National Institutes of Health that initially reported favorable responses to lymphopheresis extended their work in a controlled trial.[26] Patients were treated with either lymphopheresis or removal of an equivalent small volume of plasma without lymphocytes. This study was carried out with both patients and physicians unaware of the treatment regi-

men used. Six patients were in each group and no strict program of rest or physical therapy was prescribed. Lymphopheresis was extensive, with 15 procedures done over five weeks; a 60 percent reduction in lymphocytes was achieved. The authors found a statistically significant reduction in objective parameters of synovitis, such as the number of swollen joints. There also appeared to be some reduction in morning stiffness. The authors concluded, however, that although statistically significant, the improvements were rather modest and probably would not justify such a cumbersome and expensive form of treatment.

A recent double-blind controlled trial of lymphoplasmapheresis has generated similar findings.[27] Seven patients in each group were treated with nine real or sham procedures in a period of three weeks. Lymphocytes were depleted by 30 percent in the treated group. At a single time point immediately following the treatment course, a statistically significant improvement in objective parameters of disease activity was noted in the treated patients. No longer-term data were reported, however, and the modest benefit seen does not justify the widespread use of this therapy for patients with rheumatoid arthritis.

Renal Disorders

Glomerulonephritis associated with hemoptysis (Goodpasture's syndrome) is a disease for which plasmapheresis therapy seems rational. The anti-GBM (glomerular basement membrane) antibody is presumed to be pathogenic and there is evidence that the period of antibody synthesis is self-limited. One would then need to protect the kidney from damage only during a brief period of time. Plasmapheresis led to response in three oliguric patients in one report but anuric patients failed to respond.[28] Pulmonary hemorrhage responded very quickly in all five patients in whom it was present. There appeared to be a correlation between the ability to reduce anti-GBM antibody titers and clinical response. In reviewing the literature, I have found 48 patients reported with a 50 percent response rate. The literature confirms that oliguric patients do better than those with anuria. Some of the results appear impressive, and patterns of response, relapse and re-response to plasmapheresis have been reported. Although the data are anecdotal and uncontrolled, the consensus of nephrologists is that plasmapheresis is a useful therapy for Goodpasture's syndrome. This notion has been challenged, however.[29] It has been observed that the response in pulmonary hemorrhage does not correlate with reduction in anti-GBM titer and that occasionally pulmonary hemorrhage will stop with no reduction at all in antibody titer. Other therapies for pulmonary hemorrhage, such as nephrectomy, are not associated with a reduction in antibody titer. This raises the question of how plasmapheresis works in this situation. It has also been observed that administering a high-dose bolus of methylprednisolone can apparently stop lung hemorrhage; it may be that physicians are now seeing a milder spectrum of Goodpasture's disease and that some of the apparent responses might represent spontaneous remissions.

TABLE 3.—*Disorders for Which Plasmapheresis Should Be Used in Primary Management*

Thrombotic thrombocytopenic purpura
Hyperviscosity syndrome
Posttransfusion purpura

TABLE 4.—*Disorders in Which Plasmapheresis Is Useful in Selected Patients*

Hematologic
Refractory immune cytopenic disorders
Idiopathic thrombocytopenic purpura
Autoimmune hemolytic anemia
Pure erythrocyte aplasia
? Immune neutropenia
Circulating inhibitors of coagulation
Cryoglobulinemia
Aplastic anemia (due to IgG)
? Light-chain nephropathy (myeloma)
Anti-Rh factor immunization
Rheumatic
Refractory systemic lupus erythematosus
Renal
? Goodpasture's syndrome
? Rapidly progressive glomerulonephritis
Adult hemolytic-uremic syndrome
Acute renal transplant rejection
Neurologic
Myasthenia gravis
Polyneuropathy with paraprotein
? Guillain-Barré syndrome
Other
Poisoning
Hypercholesterolemia

Plasmapheresis has also been used for rapidly progressive glomerulonephritis that is not associated with anti-GBM antibody. This disorder is presumed to be caused in many cases by immune complexes, and it has been suggested that the presence of immune complexes may be short-lived. One study reported response in five of nine patients with this condition and saw occasional patients with response, relapse and re-response patterns.[30] In reviewing the literature, I have found 29 cases of rapidly progressive glomerulonephritis with a 66 percent response rate. However, recent reports of six of nine patients responding to the administration of a high-dose bolus of methylprednisolone raise the question of whether that much simpler therapy might be equally effective.[31] At this point, the role of plasma-

pheresis in the treatment of rapidly progressive glomerulonephritis remains controversial.

Neurologic Disorders

Plasmapheresis has great usefulness in the treatment of myasthenia gravis. In this disorder, antibodies against the acetylcholine receptor have been reported in more than 90 percent of cases. The disease is a prototype of an antibody-mediated disease that can be passively transferred by serum and in which the neonate is occasionally affected. One study reported on five patients with myasthenia who were failing to respond on conventional therapy with thymectomy and administration of prednisone and anticholinesterase drugs.[32] All five patients responded to treatment with plasmapheresis, and antireceptor antibody titers were reduced 80 percent (70 percent to 85 percent). For individual patients, there was a good correlation between change in antibody titers and disease activity. One interesting observation was that antireceptor antibody levels fell to a far greater extent than total IgG. The authors hypothesized that the use of azathioprine, in conjunction with plasmapheresis, selectively eliminated the clone of cells that was accelerating antibody synthesis in response to depletion. This remains a hypothesis. Other groups have confirmed the high response rate of patients with myasthenia to apheresis, and plasmapheresis is widely accepted in the treatment of myasthenia and is useful in several different situations, including patients with refractory disease, those with myasthenic crisis and those about to undergo thymectomy or initiation of treatment with prednisone.

Summary

There are only a small number of diseases for which plasmapheresis is the treatment of choice in their primary management (Table 3). These would include thrombotic thrombocytopenic purpura, the hyperviscosity syndrome due either to macroglobulinemia or myeloma, and posttransfusion purpura. The latter is a rare hemorrhagic disease with a high mortality and with a poor response to conventional therapy such as prednisone administration.

There are a number of diseases in which plasmapheresis is useful in selected patients (Table 4). In hematologic diseases of immune origin such as idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia and pure erythrocyte aplasia, plasmapheresis should be applied to patients with serious disease that have failed to improve on conventional therapy. Although there are no reports of the use of plasmapheresis in the treatment of immune neutropenia, the same rationale would apply. Plasmapheresis is also useful in the treatment of circulating inhibitors of coagulation, particularly spontaneously acquired factor VIII inhibitors. Among the rheumatic diseases, the only clear-cut indication for apheresis is in systemic lupus erythematosus when the disease progresses despite maximal conventional therapy. Among the renal diseases, Goodpasture's syndrome should probably be treated with plasmapheresis, as should adult hemolytic-uremic syndrome, which is a variant of thrombotic thrombocytopenic purpura. The role of plasmapheresis in the treatment of rapidly progressive glomerulonephritis remains controversial. Among the neurologic diseases, in addition to myasthenia gravis, occasional cases of polyneuropathy associated with a paraprotein have been reported to respond to apheresis. In some of these cases, the paraprotein has been shown to bind to myelin in vitro and is presumably pathogenic. Acute febrile polyneuritis (Guillain-Barré syndrome) has been reported to respond dramatically to the use of plasmapheresis. However, in a disease that spontaneously remits, controlled studies are necessary. The University of California, San Francisco, is now participating in a multiinstitution randomized cooperative study to assess the role of plasmapheresis in the treatment of Guillain-Barré syndrome.

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Medical Practice Questions

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Plasmapheresis for Rheumatoid Arthritis

QUESTION:

Is lymphopheresis, plasmapheresis or lymphoplasmapheresis considered accepted treatment in patients with rheumatoid arthritis who either

- *meet* both *of the following two criteria:*
  (1) *classical or definite rheumatoid arthritis and*
  (2) *chronic but potentially reversible severe erosive inflammatory synovitis, previously unresponsive to an adequate trial of gold, penicillamine or hydroxychloroquine* or
- *have acute life threatening complications, such as malignant vasculitis, hyperviscosity and cryoglobulinemia?*

OPINION:

In the opinion of the Advisory Panels on Allergy, Internal Medicine and Orthopedics, plasmapheresis may be beneficial treatment for highly selected patients with rheumatoid arthritis when such treatment is performed under a well-defined protocol with patient informed consent at a well-established and experienced facility.

Though it still must be considered an investigational modality in most instances, it may be considered acceptable treatment for certain patients with classical or definite rheumatoid arthritis who have acute, life-threatening complications, such as malignant vasculitis, hyperviscosity and cryoglobulinemia.

Therapeutic pheresis for the treatment of rheumatic diseases should be restricted to the above conditions and should *not* be accepted as standard medical treatment at this time.

Clinicopathologic Conference

Fever and Leukopenia in a 2-Year-Old

Moderator
STEPHEN A. SPECTOR, MD

Discussants
CAPT PHILIP GOSCIENSKI, MC, USN; STEPHEN A. SPECTOR, MD; SASKIA HILTON, MD, *and* BETH KLEINER, MD

STEPHEN A. SPECTOR, MD:* *This conference will deviate from the usual Grand Rounds format in that the case to be presented is unknown to the discussant. Dr Beth Kleiner will summarize the findings in this case.*

BETH KLEINER, MD:† This was the first University Hospital admission for this 2-year-old Mexican-American female infant who was admitted because of fever and lethargy.

Report of the Case

The child was well until four days before admission, when a fever to 40°C (axillary) and vomiting developed. Three days before admission she was seen in a medical clinic in Los Angeles where her pharynx was noted to be erythematous and she was treated with intramuscular administration of penicillin. Oral penicillin therapy was also initiated, which was continued daily until admission.

The child's appetite was decreased, but she took fluids well. She continued to have fever and was seen at a community health care center the day before admission. Her pharynx was erythematous and exudates were present. She again was treated with intramuscular administration of penicillin and advised to continue taking oral penicillin.

On the day of admission, the child was seen again at the community clinic. Emesis had stopped, but she began to have diarrheal bowel movements without gross blood. She appeared lethargic and acutely ill and was referred to University Hospital.

The medical history was unremarkable. The child was the normal product of a full-term pregnancy and weighed 3.5 kg at birth. She had grown and developed normally and had no previous medical problems. Her immunizations were up to date. A tuberculin skin test 1½ months before admission was negative. There was no family history of tuberculosis. No family members had recently been ill. The patient lived with her natural parents in San Ysidro; they all frequently visited Mexico.

On physical examination, she was a pale and lethargic child. Her weight was 9.5 kg. The pulse rate was 125 per minute, the blood pressure was 80/60 mm of mercury, the respirations were 22 and the temperature was 40.8°C. The head was normocephalic. There was no conjunctivitis, the sclerae were nonicteric and the fundi were normal. There was no nasal discharge. Tympanic membranes were normal. The mucous membranes were dry; there was a blister on the right dorsal area of the tongue, and her lips were cracked. The pharynx was red, and there was white material on the tongue. The neck was supple; there was some anterior cervical lymphadenopathy. The chest was clear to percussion and auscultation. The heart was normal. The abdomen was soft and bowel sounds were normal. The liver was palpable 1 cm below the right costal margin and the spleen tip was palpable. There were no masses, guarding or tenderness. Rectal examination was negative. Culture of a stool specimen was positive for occult

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blood. The extremities were cool. There was no cyanosis, clubbing or edema. The child was extremely lethargic, but her cranial nerves were intact and her reflexes were symmetric.

Laboratory studies disclosed the following values: The serum concentration of glucose was 122, blood urea nitrogen 15 and creatinine 0.6 mg per dl; sodium was 130, potassium 3.4, chloride 96 and bicarbonate 25 mEq per liter. The serum aspartate aminotransferase (formerly SGOT) was 71 IU. The peripheral leukocyte count was 3,400 per cu mm with 41 percent polymorphonuclear leukocytes, 38 percent band forms, 18 percent lymphocytes, 2 percent monocytes and 1 percent metamyelocytes. The hemoglobin level was 10.3 grams per dl and the hematocrit 30 percent. The platelet count was 70,000 per cu mm. Urine analysis showed a specific gravity of 1.025, a pH of 5.5, 2+ protein and two to five leukocytes per high power field. The cerebrospinal fluid contained one lymphocyte, no erythrocytes, protein level of 7.0 and glucose level of 67 mg per dl. Gram stain was negative for bacteria. A roentgenogram of the chest showed no abnormalities. An abdominal film showed slightly dilated loops of bowel with no masses and no free air.

An electroencephalogram showed generalized slowing. The patient remained febrile to 39°C and was profoundly lethargic. A repeat blood count showed a leukocyte count of 1,700 per cu mm with 13 percent polymorphonuclear leukocytes, 23 percent band forms, 54 percent lymphocytes, 9 percent monocytes and 1 percent metamyelocytes. The hemoglobin level fell to 8.3 grams per dl. The reticulocyte count was 0.1 percent and the platelet count fell to 24,000 per cu mm. The prothrombin time, partial thromboplastin time and fibrinogen in the serum remained normal. Treatment with administration of ampicillin and chloramphenicol was continued. Bone marrow aspiration on the second day showed decreased cellularity and decreased numbers of megakaryocytes. Myeloid maturation was normal. An abdominal ultrasound examination showed mild hepatosplenomegaly and a small amount of free peritoneal fluid. A contrast roentgenographic study was carried out.

DR SPECTOR: *The roentgenographic findings will be presented by Dr Hilton.*

SASKIA HILTON, MD:* Before I present the findings of the roentgenographic studies, let me summarize the problem with which we were presented. A 2-year-old female infant was febrile and had a history of vomiting. Although her stool was not frankly bloody, it had been positive for occult blood. She had no evidence of an abdominal mass, but on ultrasound was found to have peritoneal fluid. The clinical impression was that she had colitis, but it was necessary to rule out the possibility of a surgical lesion, specifically, appendicitis or intussusception. The barium enema study was done, therefore, not to evaluate a possible colitis, but to exclude a surgically correctable illness.

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Roentgenographic Findings

The plain roentgenographs showed multiple loops of mildly dilated bowel. Cross-table views confirmed that there was no free intraperitoneal air, indicating that perforation of the bowel had not occurred and that the patient did not have a toxic megacolon.

The barium enema study showed a normal colon with the exception of the ascending segment. An intussusception was not present and the appendix was normal. The rectum was normal and without spasm, thereby excluding congenital megacolon (Hirschsprung's disease). The ascending colon showed pronounced mucosal edema, which could be seen as apparent mucosal masses projecting into the bowel lumen. No ulcerations were present.

In summary, there was mucosal edema in the ascending portion of the colon. The differential diagnosis included colitis of any etiology, hemolytic uremic syndrome, Schönlein-Henoch purpura or submucosal bleeding in a hemophiliac patient. The most likely diagnosis was colitis. A surgical lesion had been excluded.

DR SPECTOR: *The case will be discussed by Dr Philip Goscienski.*

CAPT PHILIP GOSCIENSKI, MC, USN:† In undertaking a conference in which the format is that of a clinicopathologic conference, the discussant has two objectives: one is to make the correct diagnosis, and the second is to make it a worthwhile teaching exercise.

Discussion

It is certainly important to make a correct diagnosis in a patient as ill as this child. This 2-year-old girl had a four-day history of high fever and vomiting. Her symptoms did not improve after she was given penicillin. Instead, she continued to have a high fever, becoming somewhat dehydrated and lethargic. The findings of the physical examination were not consistent with the history that her growth had been normal. At 24 months of age, I would have expected her to be a little heavier than 10 kg (23 lb), which would have been her rehydrated weight. The lethargy mentioned in the history I have considered a strong clue. The fact that meningism was not described does not assure me that it was not present, but I must assume that to be the case. I accept the finding that the cranial nerve examination was also normal. She was dehydrated and had an inflamed pharynx. The pulse rate was not very high in view of the apparent severity of her illness. One wonders if there was contact with animals, or if there was any particular reason why a tuberculin skin test was done a few weeks before this present illness. If she was not entirely well until four days before admission, as the history told us, there must have been a preceding illness that might have indicated the need for a tuberculin skin test.

Her hematologic findings were interesting. On admission, she had leukopenia but did not have a neutro-

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penia. The absolute neutrophil count was over 2,600 per cu mm, which is normal. It then declined to about 1,000 and that could be an ominous or a benign finding. The leukocyte count can only suggest or support a diagnosis. It rarely helps us to make a specific diagnosis. I believe it was helpful but not definitive in this instance.

The normal findings on the lumbar puncture study must have been reassuring to the attending physician. The likelihood of there being meningitis or encephalitis in the presence of such a normal spinal fluid is very remote. The changes in her bone marrow were considerable; all of the elements were decreased. We do not know if she had taken chloramphenicol before admission, but I do not believe chloramphenicol toxicity contributed to this child's illness. Idiosyncratic marrow aplasia usually does not occur until two weeks or more after stopping therapy. The expected pharmacologic-hematologic changes are seldom as dramatic as those that occurred in this patient. Platelet counts rarely drop below 100,000 per cu mm and neutropenia tends not to be seen. There is an increase in the myeloid-erythroid ratio and some vacuolization of the marrow precursors, especially erythrocyte precursors. I prefer, therefore, to think that her hematologic changes occurred due to the infectious process.

The finding of a small amount of free peritoneal fluid is a tantalizing one. I wonder how far along in the course that first occurred. The dilation of the bowel noted could have represented only a mild paralytic ileus, but there is the possibility in an infant this age of an intermittent intussusception that may produce some changes, even a fairly toxic appearance at times.

The differential diagnosis in this case is long. There are relatively few entities, however, that are really good candidates to explain this child's illness. I will attempt to discuss this case as most of us would have thought it out, rejecting some diagnoses and adding others as the clinical features emerge.

A diagnosis of tuberculous meningitis in a lethargic 2-year-old must be considered, but is unlikely in a patient with these findings in the cerebrospinal fluid. Our service handles several patients yearly with tuberculous meningitis and needs always to be alert to this diagnosis. How likely is tuberculous meningitis in this patient? A negative family history is a big help, but why did she have a skin test six weeks earlier? Was there a neighborhood contact, or perhaps a babysitter or a relative from across the border? A negative tuberculin skin test really tells us very little. About half of our patients with tuberculous meningitis are skin-test negative at the time of admission. About the same can be said of the chest radiograph. Almost half of the patients with tuberculous meningitis show no radiographic evidence of pulmonary disease.[1] How about the cerebrospinal fluid? In patients with tuberculous meningitis, the cerebrospinal fluid cell count may be normal or the protein level may be normal, but it would be extremely unlikely that both would be normal in a patient with enough disease to have the symptoms she has. The historical and physical findings also lead us away from a diagnosis of tuberculous meningitis. There was no contact with persons with tuberculosis; apparent good health until four days before admission, high fever, the absence of cranial nerve findings and the absence of meningeal signs are all against it.

There is a southwestern United States disease that sometimes resembles tuberculous meningitis, and that is meningitis due to *Coccidioides immitis*. It tends to be less acute than this particular patient's illness, and the cerebrospinal fluid findings made this an extraordinarily unlikely diagnosis. Certainly any ill child may have bacterial meningitis and, despite no meningeal symptoms, it was still a possibility. However, I feel it was adequately ruled out by the normal findings from the lumbar puncture. I urge you to remember that the spinal fluid can change in a very short time; I have seen spinal fluid changes occur in a matter of six to eight hours, going from almost no cells (certainly fewer than ten mononuclear cells) to several hundred neutrophils in a relatively short period of time.

A high fever with lethargy and a red throat, no response to penicillin therapy and a "viral" leukocyte count all make a tempting case for infection with an Epstein-Barr virus. There are absolutely no diagnostic features of Epstein-Barr virus infection in small children. The mononucleosis spot test is often negative; Epstein-Barr titers are not immediately available, and atypical lymphocytes and excessive numbers of monocytes may not be present in a peripheral blood smear. In any case, a toxic-appearing, cold, clammy 2-year-old infant is not a likely candidate for Epstein-Barr virus infection unless there is some accompanying complication. In the same vein, cytomegalovirus and herpes simplex virus, though they too can produce diseases with severe and protean manifestations, are poor candidates in this particular case. When herpes simplex virus causes central nervous system disease, it leaves an identifiable trail, usually in the form of leukocytes, erythrocytes and some protein in the spinal fluid, and frequently some focal neurologic findings. Cytomegalovirus does not usually cause significant clinical illness in an otherwise healthy 2-year-old.

Shigella infection sometimes makes children quite ill. It is by no means rare for a patient to have profound fever, some vomiting and lethargy, even seizures, before the onset of diarrhea. Sooner or later there will be diarrhea, generally more serious than that described in this patient. *Shigella* may also produce some striking hematologic changes, from leukopenia to leukemoid reaction. A raised band count is fairly common, but it tends to be higher than it was in this patient. Other elements of the blood are not usually affected. When a *Shigella* infection is due to a particular serotype, *dysenteriae,* type 1, the symptoms may be more severe than the ordinary case of shigellosis. There may be a toxic megacolon. These patients sometimes have all the features of severe, acute ulcerative colitis with shock and renal shutdown. Some of these patients undergo total colectomy in the mistaken idea that they have

toxic megacolon due to ulcerative colitis. This patient did not appear to be that ill. Her abdominal findings did not seem to reveal that much illness.

I tend to lean toward a diagnosis of bacterial sepsis in this patient. There was no obvious focus. Her lethargy, cold, clammy appearance, relative hypotension and poor capillary filling suggested that antibiotic treatment should be initiated as soon as cultures were done. She was obviously also in need of fluid replacement, as indicated by many physical signs of dehydration.

A 2-year-old with high fever and leukocytosis is a good candidate for bacteremia due to the pneumococcus or *Hemophilus influenzae,* type b. This child did not have a leukocytosis; she had leukopenia, though as I mentioned earlier, she did not have neutropenia. If that blister on her tongue had been on the surface of the gingiva or hard palate, I would have considered pneumococcal bacteremia. There have been some case reports of pneumococcal bacteremia in which the patient had a bullous lesion of the mucosa either on the surface of the gingiva or on the hard palate.[2] As far as I know, in only one of those patients has there been histologic and bacteriologic examination of the lesion, and no organisms were seen there. However, I do not think that this patient had sepsis due to pneumococcus or *H influenzae.*

Neisseria meningitidis sepsis tends to be a fulminating process. It is generally accompanied by skin lesions that are virtually pathognomonic. Neutropenia is not only a common accompaniment of meningococcal sepsis, but it is also a poor prognostic sign. Meningitis may not be present. In fact, the absence of meningitis is also a poor prognostic sign in meningococcemia.[3]

A relative newcomer is *Yersinia enterocolitica.* Only in the past few years has this organism received attention in the medical literature. It does cause sepsis at times, but it more often causes an ileitis and mesenteric adenitis, with or without diarrhea.[4] That could explain her peritoneal fluid seen on ultrasound study. A history of animal contacts would have been helpful. There have been two family outbreaks of serious disease due to *Y enterocolitica* associated with household dogs.

In the Southwest, another *Yersinia, Yersinia pestis,* the plague bacillus, must also be considered in the differential diagnosis of what appears to be sepsis. *Y pestis* may be transmitted by dogs and cats, and there is no need for an insect vector.[5] Against the possibility of plague septicemia in this case is the absence of pneumonia, which is likely to be present if there is no vector. Even though I do not think this child had sepsis due to *Y pestis,* it is always an important disease to consider, particularly in California.

What impressed me most about this child was the triad of lethargy, high fever and leukopenia. My diagnosis then was sepsis, and the lethargy or the stupor that occurred in this patient is the symptom on which I would base my diagnosis. The Greek word for stupor is *typhos,* and the diseases typhus and typhoid (which means "typhos-like") are similar enough so that they were not clearly differentiated from one another until about 150 years ago, even though they both wreaked havoc on humanity for hundreds, perhaps thousands, of years. Typhus has disappeared from this country; typhoid has not. It will continue to occur in any population whose way of life includes poor sanitation. It has been said a number of times that the relative disappearance of typhoid from the United States could be attributed to the plumbers of our country rather than to the physicians.

What supports the diagnosis of typhoid in this patient? In addition to the fever and lethargy, she had several of the findings noted in children with this disease—vomiting, mild diarrhea, a relatively normal pulse rate, an erythematous pharynx, mild splenomegaly and guaiac-positive stools. That all sounds consistent with a viral illness but the changes in sensorium and the hematologic changes point toward a more serious diagnosis. It would have been nice to know if rose spots had developed. Many patients with typhoid have rose spots, but they may not appear until about the second week of illness, when a convalescing, afebrile patient may not be examined daily. Rose spots may be very few in number, perhaps fewer than ten, and a physician who has never seen one may not recognize them. If a patient's skin is fairly dark, rose spots may be practically invisible.

Febrile agglutinin titers are practically worthless in the diagnosis of an acute illness. They may be negative at the acute stage, and some patients may have a positive titer due to past infection or immunization. Not only are several days required for a diagnostic fourfold titer, but in some patients with untreated typhoid a rise in febrile agglutinins never occurs.[6]

In 1937 Harry Dietrich[7] summarized the findings in 60 children with typhoid at Los Angeles Children's Hospital. The youngest patient was 21 days old. Symptoms were frustratingly nonpathognomonic: fever, abdominal pain, vomiting, headache, malaise, drowsiness, diarrhea, constipation and delirium. They occurred in 20 percent or more of the patients. But none of the patients had all of these symptoms, and some patients had no fever. Central nervous system symptoms were prominent and included intractable irritability, stupor and coma.

Physical findings were not much help either. Most patients had rose spots, but not until late in their disease. Many had hepatosplenomegaly, though 25 percent did not. Falling leukocyte counts were common, but no patients in that group had a bone marrow examination. Absence of diarrhea does not rule out typhoid fever; constipation is common. Stool cultures are often negative until the end of the third week of illness, but in 85 percent they were eventually positive in that 1937 study.

Of course, in 1937 none of those patients received antibiotics. They remained febrile from one to seven weeks. Some of the fevers were sustained; some were irregular. Three patients died, one of probable Gram-

negative shock, one of staphylococcal sepsis and one with combined problems of cerebral edema and myocarditis.

Almost 30 years after Dietrich's paper, a report appeared of a typhoid epidemic in Scotland.[8] There were 507 patients, 86 of them children. These were of middle- and upper-class families in Aberdeen whose infection came from the meat counter of a supermarket. The fact that this was a healthy population that received early treatment is an important factor, and might well explain why that epidemic was so benign; there were no deaths among the 86 children. Again, as in 1937, typhoid was a nonspecific illness. The symptoms were mild but keep in mind that those patients were identified by positive stool cultures and some of them (15 of 86) were entirely asymptomatic.

In the treatment of typhoid, ampicillin and chloramphenicol are both effective agents, but patients treated with chloramphenicol may have a higher relapse rate.[9] For example, in the early 1970s, there was an outbreak of typhoid in a Florida migrant labor camp.[10] More than 100 children were treated with chloramphenicol. The relapse rate was 6.8 percent, but there were no relapses in those patients receiving ampicillin. About ten years ago an epidemic of typhoid fever began in Guatemala and spread to Central Mexico.[11] The organism was resistant to chloramphenicol but was sensitive to ampicillin. I would suggest that anyone in Southern California suspected of having typhoid, especially a toxic-appearing patient, be given antibiotics or ampicillin alone unless the sensitivity pattern is known. Trimethoprim-sulfamethoxazole therapy has been tried in typhoid with fairly good clinical results, but relapse rates may be higher than with chloramphenicol.[12]

In summary, I believe that this 2-year-old had typhoid fever, with marrow depression due to that disease. I suspect that *Salmonella typhosa* is the particular causative organism, but other *Salmonella* sps cause a typhoid-like syndrome that is indistinguishable from mild typhoid.

DR SPECTOR: *Thank you, Dr Goscienski.*

Summary

On the second hospital day, six to ten discrete papular erythematous lesions developed that were confined to the anterior chest and abdomen. These lesions initially blanched, but faded rapidly and were gone the following day. They had all the features of the rose spots found in typhoid fever. Cultures of specimens of the patient's blood and stool subsequently grew *S typhosa*.

Recently the Center for Disease Control reviewed reports of *Salmonella* bacteremia from 1968 through 1979.[13] During that 12-year period there were 8,018 organisms of 128 serotypes identified. California recorded the highest numbers of *Salmonella* organisms found in blood of any state, comprising 18 percent of the total. Six serotypes of *Salmonella* accounted for nearly 70 percent of organisms found in blood, with *S typhosa* accounting for 23.4 percent; *Salmonella typhimurium,* 20.3 percent; *Salmonella enteritidis,* 10.2 percent; *Salmonella heidelberg,* 8.9 percent; *Salmonella choleraesuis,* 3.8 percent, and *Salmonella saint-paul,* 2.6 percent. The reported identification rate in blood per million people was highest for infants younger than 1 year of age, with the peak rate in the 1-day to 2-months-old group. The incidence for 2-year-olds was about 50 per 100,000 population.

S typhosa, S enteritidis, serotype *paratyphi* A and serotype *paratyphi* B infect only humans. The incidence of typhoid fever is determined, therefore, by the prevalence of human carriers, the adequacy of environmental sanitation and the purity of the water supply. Technical improvements in handling human wastes and water have more than any other factors decreased the incidence of typhoid fever. In underdeveloped countries, however, where there is poor sanitation and contamination of water supplies, typhoid fever remains a common endemic illness.

The fact that *S typhosa* infects only humans theoretically should facilitate efforts to eliminate typhoid fever. Vaccines of killed typhoid organisms have been used since the late 19th century, though their efficacy was not established until the 1960s. Field trials in Guyana showed that the heat-, phenol- and acetone-inactivated vaccines are 65 percent to 90 percent effective in preventing typhoid fever.[14] Although typhoid fever usually confers lifelong immunity, the nature of protection is unknown. The titers of antibodies against O, H and Vi antigens have not been connected with protection. Naturally occurring sources of *S typhosa* usually contain 100,000 organisms. Volunteer studies indicate, however, that vaccine-acquired immunity can be easily overcome with a challenge of 50 percent infectious dose (10 million) of *S typhosa* organisms.[15] The effectiveness of *paratyphi* A and B vaccines has never been established, and they are not recommended for use either individually or in combination with typhoid vaccine. Typhoid vaccine in the United States is not recommended for general use, and is not indicated for controlling common source outbreaks or in natural disasters.[16]

As Dr Goscienski said, there are three drugs—ampicillin, chloramphenicol and trimethoprim-sulfamethoxazole—that favorably influence the outcome of typhoid fever. This child was treated with both ampicillin and chloramphenicol and recovered rapidly. On follow-up examinations, she had no evidence of relapse.

PHYSICIAN IN THE AUDIENCE: *Can you comment on the thrombocytopenia observed in this patient?*

DR SPECTOR: Abnormalities of clotting studies, including thrombocytopenia, hypofibrinogenemia and increased levels of circulating fibrin-split products, have been reported in over 50 percent of patients with typhoid fever. This patient's platelet count fell to 24,000 per cu mm on the second day of hospital stay. While receiving

adequate antibiotic therapy, her platelet count rose to over 100,000 per cu mm by the fourth day of hospital stay.

PHYSICIAN IN THE AUDIENCE: *How common is pharyngitis with typhoid fever?*

DR SPECTOR: Pharyngitis is well described in association with typhoid fever. The reported incidence, however, is quite variable. In the preantibiotic era, in one large study more than 10 percent of patients had sore throats associated with typhoid fever. In a recent outbreak of typhoid fever, only 5 percent of patients had a sore throat. It is important to remember that the initial clinical manifestations of typhoid fever in children as well as adults frequently mimic an upper respiratory tract infection. Fever, headache, cough and cervical adenopathy, as well as pharyngitis, are common. Respiratory findings including rales on auscultation are frequently present.

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Medical Staff Conference

Women's Curse: A General Internist's Approach to Common Menstrual Problems

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs David W. Martin, Jr, Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR. SMITH:* *It is a pleasure to introduce our next speaker to this conference, who is now finishing up her Chief Residency at Moffitt Hospital. Dr Carol Jessop received her undergraduate degree from Stanford and her medical degree from the University of California, San Francisco. Following graduation, she went to the Massachusetts General Hospital for three years before returning here as Chief Medical Resident. She will join the faculty next year with the special responsibility of coordinating our student clerkships. Dr Jessop was recently honored as co-recipient of an award as the outstanding woman house officer in Northern California. She will speak on "The Woman's Curse: A General Internist's Approach to Common Menstrual Problems."*

DR JESSOP:† Thank you, Dr Smith, for that very nice introduction. "Women's curse"—that is the phrase we so commonly use whenever we are describing the menstruation process and the problems associated with it. Since the beginning of human life, the menstruation process has set women apart from men in a mysterious and almost magical way. Women's blood flows naturally, rather than being the usual indication of injury or death that other blood flow is. It comes and goes with a regularity that is usually interrupted only by the creation of human life.

Early civilizations, frightened by the unknown forces that caused women's bleeding, created a goddess of the womb. By worshipping such a goddess and her bleeding fertility, they found temporary safety from her hidden powers. But her power to create also suggested a power to destroy, and so it was that many cultures tried to tame these potential powers by ostracizing and punishing a menstruating woman and making her essentially a taboo.[1(p1)] In the Roman era, Pliny the Elder in his *Natural History* described menstruation in the following way:

> But nothing could easily be found that is more remarkable than the monthly flux of women; contact with it turns new wine sour, crops touched by it become barren, grass dies, seeds in gardens are dried up, and the fruit of trees fall off.[2]

This belief in menstrual blood as a poisonous substance was also held by the MaeEnga tribe of New Guinea. They believed that "contact with menstrual blood or a menstruating woman would sicken a man, corrupt his vital juices, permanently dull his wits, and lead to his death."[3] Even today, modern taboos, though they are less explicit, remain powerful in that they continue to suggest that a menstruating woman is a victim of her own hormonal fluctuations. Women are commonly thought to be less capable of enduring emotional and physical stress during their menstrual periods. In grammar school hygiene courses, young girls are taught that they will need to decrease their activities and get plenty of sleep during *that* time of the month. The medical profession itself has frequently labeled women with menstrual difficulties as having dependent and hysterical personalities. Medical journals in particular continue to display demeaning advertisements that promote the stigma of the "helpless, menstruating

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woman." In medical school it is common for students to be inundated with lectures on endocrinology and graphs of the menstrual cycle, but very little, if any, lecture time is devoted to the pathophysiology and medical management of water retention, dysmenorrhea and heavy bleeding. Added to this problem is the current trend of some medical schools to reduce the subject of obstetrics and gynecology to an elective course, suggesting to our students that, in fact, this area of health care is not important to master before obtaining a medical degree. It is thus understandable, and yet very regretable, that most internists (even house officers fresh out of medical school) avoid the menstrual problems and even the pelvic examinations of female patients. Instead they refer them to their colleagues who have specialized in obstetrics-gynecology and who have largely been trained to approach these problems in a surgical manner.

It was in 1868, when the first hysterectomy was done, that the medical profession finally began to address menstrual disorders. Since then, there has been a steady rise in the number of hysterectomies being carried out, and it is estimated that if this present rate continues, by 1985 50 percent of women who reach the age of 65 will have undergone a hysterectomy.[4] Because little attention has been given to the medical management of menstrual problems, this rise in the number of hysterectomies done each year should come as no surprise. According to government statistics in 1975, total abdominal hysterectomies that year numbered 725,000, compared with 685,000 tonsillectomies and 379,000 appendectomies (reported by Victor Cohn of the Washington Post, May 10, 1977). Thus, hysterectomy now surpasses the former top ranking operations in this country. It is the surgical procedure most commonly done on women except, of course, for the dilatation and curettage procedure, of which 1.7 million were done in 1975.

In light of this alarming trend, there is ample reason to wonder if all of these hysterectomies and dilatation and curettage procedures are really necessary. One study of a second surgical opinion program in New York found that 43 percent of 384 recommended elective hysterectomies were not confirmed by a second opinion. Additionally, 36 percent of 115 recommended dilatation and curettage procedures were not approved.[5] The Center for Disease Control (CDC) conducted its own survey of 3.5 million elective hysterectomies done in this country between 1970 and 1979 and concluded that one out of every seven hysterectomies was done for questionable reasons. Many of these women had been told that because their child-rearing days were over, they may just as well get rid of the "monthly problem."

Even in those cases where indications were approved, surgical procedures on 1.3 million women (27 percent of the cases reviewed) were carried out for functional diagnoses such as bleeding, pelvic pain and related mood disorders. Although one might assume that the increasing number of hysterectomies and dilatation and curettage procedures done was related to improved surveillance and cancer detection efforts, the statistics do not support this. The preoperative diagnosis given in 68 percent of the cases was "rule-out cancer," but only 6 percent had evidence of malignancy at pathology evaluation. The complication rate of hysterectomies was also thought to be high. The mortality in this operation alone was 204 per 100,000 operations done, and the CDC's study found that the morbidity rate approached nearly 50 percent. A separate retrospective study that looked at 959 patients who underwent total abdominal hysterectomy in the early 1970s found that half of the patients suffered complications: 37 percent had fever or infection, 15 percent required transfusion, 13 percent made emergency room visits after being discharged from the hospital, 3 percent required readmission to hospital, and 1 percent required unintended major surgical repair as a result of their former operation. The average convalescence period for each woman was 48 days, and there was one death reported from a presumed pulmonary embolus (Medical World News, Dec 7, 1981, p 24). Thus, it is clear that surgical treatment is not benign and should be the last resort in the treatment of disorders of menstruation.

TABLE 1.—*Symptoms of the Premenstrual Syndrome**

Tension	Acne
Depression	Bloating
Irritability	Breast congestion
Lethargy	Back pain
Headaches	Joint pain
Migraine	Urticaria

*Reprinted with permission from Dalton.[6]

Our referring patients to surgical treatment has, in fact, had a tremendous impact on our health care system. First of all, there is a growing patient dissatisfaction with parceled-out health care. Referral results in a delay in evaluation and treatment of problems, increasing medical costs and, as just discussed, an increasing number of surgical procedures and resulting complications. A review of the pathophysiology of these common menstrual disorders suggests that most will respond to medical management. Although most internists have not previously considered premenstrual syndrome, dysmenorrhea and hypermenorrhea as part of their field, there is a great need for them to begin to do so. This article will cover the topics of the premenstrual syndrome, dysmenorrhea and hypermenorrhea and their medical management.

The Premenstrual Syndrome

The premenstrual syndrome or— as it may be thought of— "the storm before the calm," is a common clinical entity that is estimated to affect 70 percent to 90 percent of women. Although not all women will experience all symptoms at once, many will report bloating and weight gain, irritability, emotional lability, headache, depression, arthralgias, back pain and breast congestion (Table 1). Many women also have an increased craving for sweets or a decreased tolerance for alcohol

just before their menstruation. Many describe a change in energy level, either up or down, and some will even report that they have had diarrhea.[6] For most women, these symptoms are merely a nuisance and a reaffirmation of their cyclic body changes. But for about 20 percent of women, these symptoms may last from the beginning of ovulation until the onset of menstruation and be so severe that they will interrupt their normal functioning at work, school or home. Several hypotheses have been proposed to explain the cause of the premenstrual syndrome. Unfortunately, many are supported only by anecdotal observations and, because of the paucity of research that has been done in this area, have yet to be confirmed by carefully controlled studies. Yet, because of more sensitive radioimmunoassays for hormones, and a better understanding of neuroendocrinology today, there are some exciting new thoughts on the horizon.

Currently the proposed causes of premenstrual syndrome are psychogenic, water retention, hypoglycemia, estrogen excess, progesterone deficiency and alterations in central nervous system neurotransmitters. The psychogenic explanation is probably the oldest of all the proposed causes of the premenstrual syndrome and it still has its proponents today. However, there are a number of physiologic changes that have been documented in women with premenstrual syndrome, and it is of no advantage to our patients to entertain the psychogenic theory further.

Water retention as a cause of premenstrual syndrome, on the other hand, is a hypothesis with which most of us are familiar. This theory postulates that estrogen, by inducing hepatic synthesis of angiotensinogen, produces a rise in levels of aldosterone with resultant sodium retention and potassium depletion. Progesterone is also thought to have an effect on total exchangeable sodium. Although it is not a consistent finding, many studies have shown that the average woman gains 1.4 kg (3 lbs) premenstrually and has a rise in her total body sodium. One of the problems with this theory, however, is that a strong correlation between premenstrual symptoms and actual increased fluid levels has not been established. Moreover, in some women symptoms such as headache, breast tenderness and abdominal bloating do not always resolve with the administration of a diuretic, suggesting that perhaps there are other factors involved.

Another theory that has received a lot of attention is that of reactive hypoglycemia. Metabolic studies have suggested that in the presence of high progesterone levels during the late luteal phase there is an increased insulin response to a standard glucose intake.[7] Investigators suggest that this might, in fact, explain the feelings of jitteriness, the mood swings, the fatigue or the increased craving for sweets that many women have just before their menses. As one might guess, however, if this were the sole mechanism of the premenstrual syndrome, then the ingestion of food would relieve these symptoms. Unfortunately, that is not the case for most women.

Another widely held view in England is that the estrogen excess and progesterone deficiency that occur premenstrually are the cause of the premenstrual syndrome. Dr Katarina Dalton, who runs a Premenstrual Syndrome Clinic in London, has been treating her patients with the administration of natural progesterone for years.[6(pp20-95)] This is not to be confused with the synthetic progestogens such as medroxyprogesterone acetate, which, according to Dr Dalton, will generally worsen the symptoms of premenstrual syndrome as they lower the plasma progesterone level. Many women in England report that they benefit from the administration of this natural hormone, but at present there are no well-controlled studies to prove its efficacy. It is also necessary to give this drug intramuscularly or via rectal or vaginal suppository. Perhaps once this natural hormone is available in an oral preparation and shown to remain biologically active, then controlled double-blind studies may be able to prove its efficacy.

Recent advances in neuroendocrinology have generated some exciting new hypotheses that suggest decreased levels of central nervous system neurotransmitters, specifically dopamine and serotonin, are the cause of the premenstrual syndrome. Early in the 1970s some investigators found transiently raised prolactin levels in women with severe premenstrual syndrome. Investigators reported that suppression of prolactin secretion by administering bromocriptine mesylate was effective in treating the mood disorders and the fluid retention. It seems unlikely though that the manifestations of this syndrome are due entirely to elevated prolactin levels, as no clear osmoregulatory role for this hormone has ever been described in human beings. Also, it would seem that patients with hyperprolactinemia would show some of the same symptoms as do women with premenstrual syndrome, but this is not the case. The reported effectiveness of bromocriptine administration may in fact not be related to its prolactin-suppressing action, but to the fact that it is a dopamine agonist. Dopamine has a direct natriuretic action on the kidney. Its role in the origin of endogenous depression is also being studied. It may be that the fluid retention, altered prolactin secretion and the mood changes that we have seen in the premenstrual syndrome are all due to decreased amounts of this brain monoamine at one or more sites, and that the positive effects of bromocriptine administration are directly related to its dopaminergic action in the kidney and in the central nervous system. Pyridoxal phosphate is a cofactor necessary in the synthesis of dopamine, and deficiency of pyridoxine has been noted in some pregnant women and women taking oral contraceptives. Some investigators speculate that premenstrual estrogens cause a relative deficiency of available vitamin B6 that results in the symptoms of premenstrual syndrome. In a recent study the effectiveness of pyridoxine replacement was tested in a double-blind crossover trial using 500 mg of the vitamin daily versus a placebo in 25 patients with severe premenstrual symptoms.[8] Striking improvement was reported in 21 of the 25 patients

though sometimes dosages as high as 800 mg a day were required. We must take note that the study did not control for factors such as a patient's dietary intake and needs to be tested with a longitudinal study involving a larger number of patients. This theory has some rationale, however, and the treatment itself is harmless.

Currently the following recommendations should be made to women who are suffering from symptoms of premenstrual syndrome:

- Reduce the dietary intake of salt and concentrated sugars. These may induce greater water retention and symptoms of hypoglycemia.
- Exercise regularly to improve one's sense of well-being and to decrease fluid retention.
- Avoid excessive alcohol intake before onset of menses.
- Take pyridoxine *daily* in doses from 200 to 800 mg a day.
- For women with severe premenstrual symptoms, add either a potassium-sparing diuretic, or administer 100 mg of natural progesterone vaginally for five days before menses.

I am hopeful that in the future, with more studies on the cause of premenstrual syndrome and the interaction of central nervous system neurotransmitters, more therapeutic options will become available.

Primary Dysmenorrhea

The number of women bothered by the problem of dysmenorrhea at sometime in their life has been estimated to be as high as 50 percent. For many of these women, dysmenorrhea can be severe enough to make them unable to attend to their tasks at work, school or at home. Although government statistics show that health-related absenteeism is less prevalent among women than men in this country, dysmenorrhea has always been reported to be the major cause of loss of work for women. One study showed that 10 percent to 15 percent of teenage girls missed one to two days of school per month due to menstrual cramps. Dysmenorrhea classically is low pelvic pain that has its onset the day before or the day of menses and completely resolves between periods. It is generally characterized as deep continuous waves of cramping that may radiate to the back or to the upper thighs. The cramps may last up to 48 hours and can be associated with nausea, vomiting and fainting. It is generally called primary dysmenorrhea when it occurs soon after the menarche and when no pathological abnormalities of the pelvic organs are found on examination. Secondary dysmenorrhea occurs later in life and is usually the result of pelvic disease such as endometriosis, cervical stenosis or pelvic inflammatory disease. For years the cause of this disorder was unknown and thus it was attributed to psychogenic origins, or the inability of a woman to adjust to her feminine role. Little importance is now given to this theory or to the position of the uterus, which historically was also suggested as a common cause of menstrual cramps.

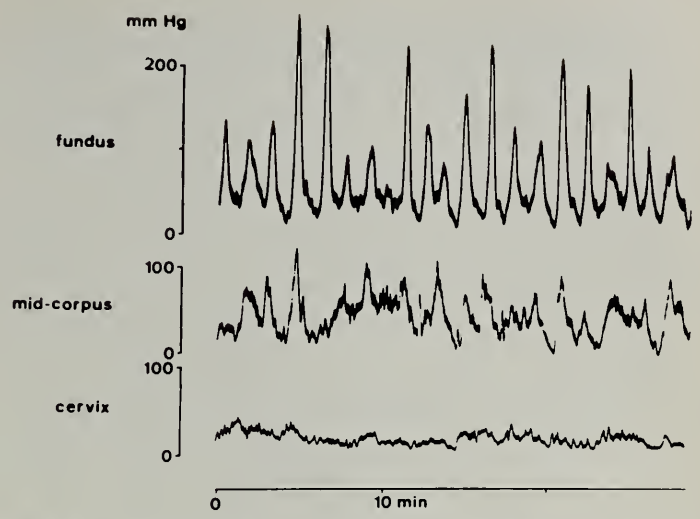

Figure 1.—Recording of intrauterine pressure with a three-channeled microtransducer catheter in a woman with severe dysmenorrhea. (Reprinted with permission from Akerlund.[9])

The factors that are considered today as possible mechanisms for dysmenorrhea are prostaglandin production, myometrial contractility, uterine blood flow, ovarian steroids, uterine innervation and abnormalities of the cervical outflow tract. Each of these mechanisms may be important if it is abnormal; some combination of these factors may be involved in patients. In 1957 a British physiologist, Dr Vernon Pickles, postulated that the menstruating uterus produces substances that play a central role in the genesis of intrauterine tonus and myometrial contractions. Although others scoffed at his idea at that time, he and his colleagues isolated a group of substances that he called menotoxins. Today they are known to be prostaglandins, specifically prostaglandin E_2 and prostaglandin $F_{2\alpha}$.

It was not until the late 1960s, however, that researchers using intrauterine balloons were able to show that each woman has her own inherent uterine motility pattern that is as unique to her as her thumbprint. Figure 1 shows a recording of interuterine pressures obtained from a woman with dysmenorrhea.[9] In studies of thousands of women during various times of their monthly cycles, women with dysmenorrhea were found to have a much more irritable uterus with profoundly increased uterine tone at the time of menses.[10] In these women, pelvic pain was found to occur whenever their interuterine pressures were higher than 50 mm of mercury and not uncommonly uterine ischemia (associated with nausea, vomiting and hypotension) would occur whenever the uterine tonus exceeded the systolic blood pressure. Dr Pickles suggested that prostaglandins may play a role in dysmenorrhea. Based on bioassay results, his group of researchers found that dysmenorrheic women produced three to four times the amount of prostaglandin $F_{2\alpha}$ in their menstrual blood than normal women, or those taking birth control pills. Figure 2 shows the different prostaglandin $F_{2\alpha}$ concentrations in three different groups of women: those without dysmenorrhea, those with dysmenorrhea and dysmenorrheic women treated with oral contraceptives.[11]

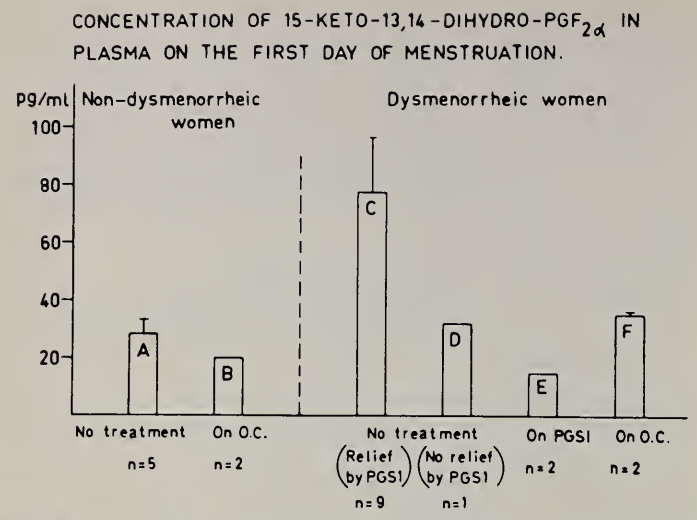

Figure 2.—Different prostaglandin $F_{2\alpha}$ levels of three different groups of women. OC = oral contraceptives, PGSI = prostaglandin synthetase inhibition. (Reprinted with permission from Lundström.[11])

There was still the question, however, of whether the increased amounts of prostaglandins seen in dysmenorrheic women were the cause of myometrial contractions, or the result. To solve this mystery, the response of dysmenorrheic women and nondysmenorrheic women to the administration of prostaglandin $F_{2\alpha}$ was studied. All women responded to pharmacologic doses of this prostaglandin with resulting uterine contractions and pain. This response was noted to be most exaggerated when the prostaglandin was administered premenstrually.[11]

In learning the importance of prostaglandins in the pathogenesis of dysmenorrhea, investigators have used nonsteroidal antiinflammatory drugs to inhibit the synthesis of prostaglandins. This class of drugs acts by inhibiting the enzyme cyclooxygenase, a key step in the synthesis of prostaglandins from arachidonic acid. Many studies have subsequently shown the effectiveness of these drugs in reducing prostaglandin levels, especially that of prostaglandin $F_{2\alpha}$, with consequent inhibition of uterine contractility and pain.[12] No single nonsteroidal antiinflammatory drug has been found to be more effective than another, though it is my experience that a woman may note a better response to or have fewer side effects with one drug than another. Therefore, it is important to try one or two before giving up. Initiation of the use of these drugs three or four days before the onset of menses has been shown to be no more effective than starting them on the day of menses. Unfortunately, there are still some women whose primary dysmenorrhea does not respond to these drugs or who are unable to tolerate the side effects from them.

If we review briefly the molecular biology of uterine contraction, it becomes apparent that there are many other sites at which we can intervene and halt the abnormal uterine contractility women have with dysmenorrhea. The following equation, in which ATPase = adenosine triphosphatase, ATP = adenosine triphosphate and Ca^{++} = calcium, demonstrates the factors that are responsible for controlling the excitation and contraction of the myofibril, which is the smallest unit of the uterine myometrium:

$$\text{actomyosin} + \text{actomyosin-ATPase} + \text{ATP} = Ca^{++} + \text{contraction}.$$

Of these factors, the two that have the highest turnover rate are adenosine triphosphate and free calcium. Theoretically, by modifying their relative concentration in the myofibril, the contraction-relaxation response should be able to be altered. Those modifications would increase ATP and calcium concentrations in the cytoplasm and cause contraction.

Figure 3 shows a more complicated scheme that represents the intracellular biology of the myofibril.[13] From our experience with other calcium-channel models, it should come as no surprise that calcium channel-blocking agents lower the amount of intracellular free calcium and cause relaxation of myofibrils. Use of a β-agonist stimulates adenyl cyclase and cyclic adenosine monophosphate-dependent phosphorylation of the binding proteins. This increases the amount of calcium-binding proteins and lowers the free calcium. Both nifedipine, a calcium channel-blocking agent, and terbutaline, a β-agonist, have been effective when administered to women with dysmenorrhea. Although terbutaline was found to be effective in inhibiting uterine contractility, resulting in pain relief within minutes, the high frequency of side effects, primarily tremor and tachycardia, has made it impossible to treat many patients with this agent.[14] The effect of nifedipine on dysmenorrhea was investigated recently in 40 women for a three-month period.[15] In all, 26 of the 40 women suggested that they had excellent pain relief; ten women had moderate relief, and four said they had no response at all. Because of the vasodilating properties of these drugs, headaches and tachycardia were frequent side effects.

Referring back to the equation, there is one more place where one can intervene, and that is by decreasing the concentration of adenosine triphosphate available intracellularly. One way to do this would be to promote more adenosine triphosphate hydrolysis by actomyosin-adenosine triphosphatase, and this has been done by increasing the concentration of magnesium. This seems to speed up the hydrolysis process and decrease the adenosine triphosphate concentration. Some investigators believe that this may be another method of treating dysmenorrhea, and have suggested to their patients that they take high concentrations of both magnesium and pyridoxine because that seems to increase the influx of magnesium into the cell. Although the effects are not as immediate as with the administration of nifedipine or terbutaline, preliminary studies have suggested that 200 mg of magnesium and of pyridoxine taken daily result in a progressive decrease in the intensity of menstrual cramps.

In summary, there are now several agents available whose administration can treat dysmenorrhea effectively: nonsteroidal antiinflammatory drugs; oral contra-

ceptives; magnesium, 200 mg daily, and vitamin B_6, 200 mg daily; nifedipine, and terbutaline.

Hypermenorrhea

The last topic I will cover is that of excessive menstrual bleeding, or hypermenorrhea.

This, too, represents a significant problem in that it results in a number of patient visits to physicians or hospitals each year. Dysfunctional uterine bleeding accounts for approximately 30 percent to 40 percent of all gynecologic outpatient visits. It is estimated that nearly 60 percent of all dilatation and curettage procedures are done for either hypermenorrhea or dysfunctional uterine bleeding.

For most patients the experience of losing an excessive amount of blood during menstruation can be not only frightening—it is also inconvenient. For many patients there may also be some hidden concerns such as pregnancy, infertility, infection, cancer or contraceptive complications. Therefore, it is mandatory that we physicians be sensitive to these issues, and that we keep in mind the most common causes of vaginal bleeding for a particular patient's age.

Table 2 lists the important causes of abnormal vaginal bleeding,[16] but it does not break them down into age groups, which I think is important to do. For example, in an adolescent patient the most likely cause of vaginal bleeding is infection, hematologic disturbances or dysfunctional uterine bleeding. Once infection, pregnancy or hematologic disturbances are ruled out, then dysfunctional intrauterine bleeding is the most likely reason for heavy bleeding. Because many of these patients have an immature hypothalamic pituitary axis, anovulation is common. In a typical *anovulatory cycle,* the endometrium is constantly stimulated by unopposed estrogen. This problem can be prevented by administering a progestogen preparation for five days each month.

For women in their reproductive years, a more

TABLE 2.—*Important Causes of Abnormal Vaginal Bleeding**

- Anatomic lesions
  - Uterine fibroids
  - Cervical erosion
  - Cervical polyps
  - Retained products of gestation
  - Ectopic pregnancy
  - Carcinoma of the endometrium
  - Carcinoma of the cervix
  - Ovarian neoplasms
- Dsyfunctional bleeding
  - Immaturity or senescence of the hypothalamic-pituitary-ovarian axis
  - Inadequate luteal phase
  - Ovarian senescence
  - Endometriosis
- Inflammation
  - Pelvic inflammatory disease
  - Intrauterine devices
- Endocrine disturbances
  - Hyperthyroidism
  - Hypothyroidism
  - Oral contraceptive use
- Hematologic disturbances
  - Bleeding diatheses
  - Iron deficiency
  - Anticoagulation therapy

*Reprinted with permission from Gorroll.[16]

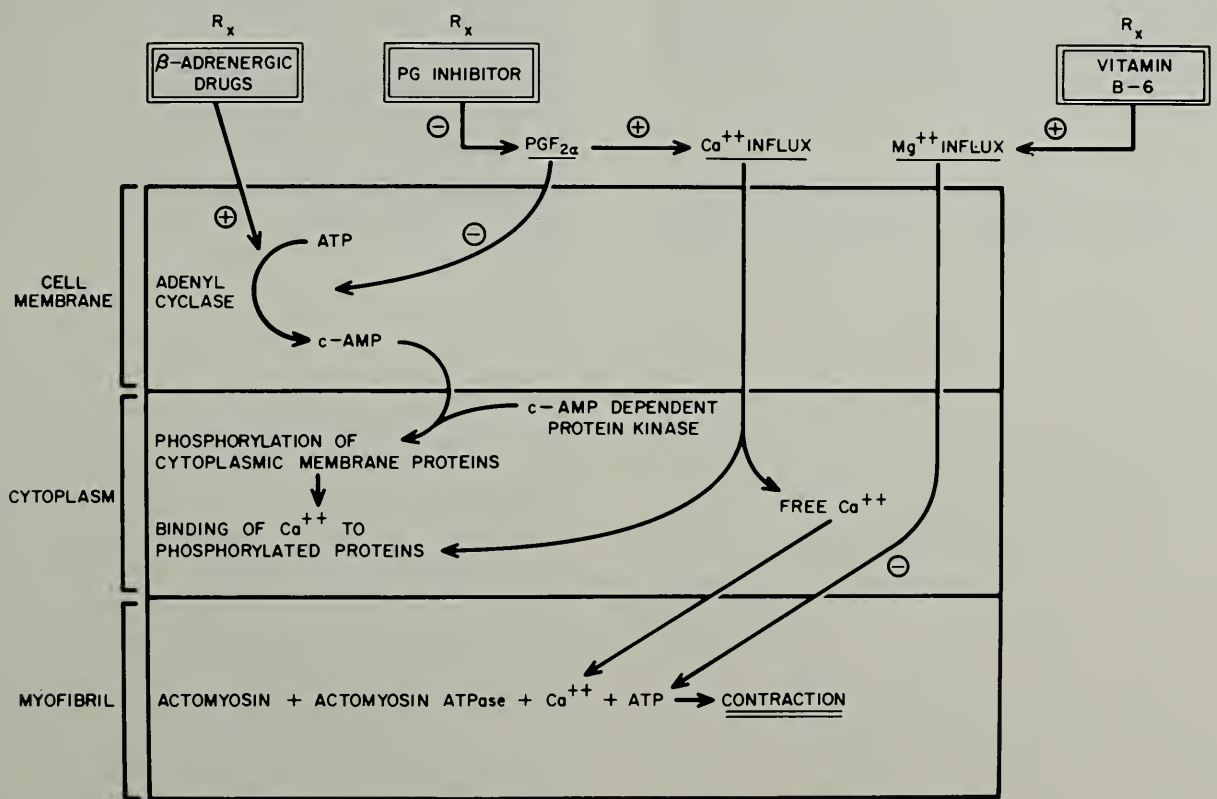

Figure 3.—Contractility model. (Reprinted with permission from Abraham.[13])

thorough workup is in order, particularly if their history and findings from a physical examination suggest an endocrine problem. Women in this age group most commonly have abnormally heavy bleeding in association with infection, contraceptive complications, iron deficiency anemia or anovulatory bleeding due to emotional stress or an inadequate luteal phase. Neoplasm is not common. An evaluation in this age group is more likely to uncover an endocrinologic cause.

In perimenopausal and postmenopausal women the three most common causes of abnormal menstrual bleeding are neoplasm, fibroids and endometrial hyperplasia that occurs before ovarian atrophy (menopause). A patient who is postmenopausal and has risk factors for endometrial cancer requires examination of an endometrial specimen obtained by suction endometrial biopsy or dilatation and curettage. But for the women who are likely having anovulatory breakdown bleeding because of impending menopause, I would prescribe medroxyprogesterone acetate for five to seven days a month so that endometrial hyperplasia does not develop. Both endometrial hyperplasia and cancer in situ may be reversed with the administration of medroxyprogesterone.

For patients with excessive bleeding due to uterine fibroids documented by examination or ultrasound studies, I would attempt using a nonsteroidal antiinflammatory drug. Women with hypermenorrhea due to an intrauterine device, dysfunctional uterine bleeding or fibroids have higher levels of prostaglandin E. This type of bleeding is very responsive to administration of prostaglandin synthesis inhibitors.[17] In treating hypermenorrhea and dysfunctional uterine bleeding, the most important point is to identify the problems of the age group, decide which patients are really at risk for cancer and try either hormonal manipulation or the nonsteroidal antiinflammatory drug before referring a patient for surgical intervention.

Conclusion

I would like to reemphasize that the problems I have been discussing are quite prevalent and involve complex biologic processes that have yet to be unraveled. There remains a tremendous need for more basic science research and clinical studies in this area. It may be even more important for us as internists to regain our interest in the management of women's menstrual disorders. The elective use of hysterectomy as a "final solution" is to be decried except when absolutely necessary. I think that we as internists have a lot more to offer our women patients with these problems, and I am hopeful that we will give them no less than our best attention and continuing interest.

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Epitomes

Important Advances in Clinical Medicine

Emergency Medicine

The Scientific Board of the California Medical Association presents the following inventory of items of progress in emergency medicine. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in emergency medicine that have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Emergency Medicine of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Verapamil and Supraventricular Tachycardia

VERAPAMIL, a calcium channel blocking agent recently approved by the Food and Drug Administration, slows conduction through the atrioventricular (AV) node. It aids in the management of most forms of supraventricular tachycardia and is considered by many to be the drug of choice for treatment of uncomplicated paroxysmal supraventricular tachycardia. In numerous clinical trials intravenous administration of verapamil has been shown in more than 90 percent of cases to convert paroxysmal supraventricular tachycardia to normal sinus rhythm within two minutes following drug administration. Long-term oral administration of verapamil for patients with frequent episodes of paroxysmal supraventricular tachycardia has been shown to decrease both the incidence and the duration of the episodes.

Verapamil therapy rapidly decreases the ventricular response rate to atrial fibrillation or flutter. Ventricular rates begin to slow immediately and maximum drug effect occurs 3½ minutes after drug administration. Therefore, though verapamil rarely converts atrial fibrillation or flutter, it may be quite valuable in the acute management of these dysrhythmias. In recent studies, verapamil given orally appears superior to digoxin administration in reducing resting and exertional heart rates while maintaining exercise tolerance in patients with chronic atrial fibrillation.

Verapamil therapy is not effective in treating supraventricular dysrhythmias that are caused by increased atrial automaticity, such as multifocal atrial tachycardia. Nor is it helpful in managing sinus tachycardia. It is ineffective in treating ventricular ectopy or tachyarrhythmias. Electrophysiologic studies have shown varying effects on the accessory pathways of patients with Wolff-Parkinson-White syndrome. Reports of increased accessory pathway conduction have resulted in the recommendation that verapamil should not be used in patients with Wolff-Parkinson-White syndrome who have paroxysmal atrial fibrillation or flutter or paroxysmal supraventricular tachycardia with a widened QRS. Nevertheless, it is highly effective in narrow-complex paroxysmal supraventricular tachycardia associated with the Wolff-Parkinson-White syndrome.

Other contraindications to the use of verapamil include sinus node disease; evidence of AV node disease; impaired cardiac contractility (moderate to severe congestive heart failure, particularly when it is not related to a transient increase in heart rate); hypotension, or possible inability to tolerate a transient 10 to 15 mm of mercury drop in systolic blood pressure, and concurrent intravenous use of β-blockers (when given concomitantly these drugs have systematically produced considerable left ventricular dysfunction and on several occasions have resulted in severe AV block leading to asystole).

The incidence of reported severe adverse effects has been less than 1 percent. In a number of instances, however, intravenous verapamil therapy has resulted in hypotension or bradycardia of sufficient magnitude to require pharmacologic interventions. In most of these cases, hypotension has responded to the administration

of norepinephrine or other pressor therapy, and bradycardia has resolved with either atropine or calcium administration.

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Pneumatic Antishock Trousers

THE USE OF DEVICES producing external counterpressure on the lower extremities and abdomen has become widespread since the dissemination of reports documenting their efficacy in controlling hemorrhage and hypervolemic shock during the Vietnam War. Military antishock trousers (MAST) were used most commonly with injuries to the lower extremities, pelvis and abdomen. Many subsequent reports have verified the device's effectiveness in similar types of trauma in civilians. External counterpressure is particularly beneficial in stabilizing patients with pelvic and lower extremity fractures; not only are the fractures splinted, but the bleeding sites about the injured area are tamponaded by the inflated garment, preventing excessive blood loss.

Hypotension due to volume maldistribution, such as in spinal cord trauma, drug effects or dysfunction of the sympathetic nervous system (as in autonomic neuropathies), will also often respond to the application of pneumatic trousers. Recent data suggest as well that abdominal binding, such as that produced by pneumatic trousers, can improve the efficacy of cardiopulmonary resuscitation during external cardiac massage. The probable mechanism for the increase in systolic blood pressure and carotid blood flow seen after MAST application is increased intrathoracic pressure during chest compression due to limitation of diaphragmatic descent by abdominal binding.

External counterpressure produces a number of physiologic effects in addition to tamponade of external and internal bleeding sites located under the garment. These include increased central venous pressure, increased peripheral vascular resistance, mild lactic acidosis (with prolonged inflation), clinically insignificant effects on renal and pulmonary function and increased carotid blood flow. Although "autotransfusion" of about a liter of blood from the lower extremities and abdomen to organs above the diaphragm was once thought to occur, recent data have shown no increase in cardiac output, stroke volume or pulmonary diffusing capacity, corresponding to the earlier findings of Tenney and Honig during ballistocardiography. This suggests that the intravascular transfer produced by the device is minimal, at most only 250 to 300 ml. Mechanisms other than autotransfusion, such as increased afterload produced by compression of vasculature in areas covered by the trousers, are a more likely basis of their effectiveness in the treatment of hypotension.

Contraindications to the use of antishock trousers include congestive heart failure and pulmonary edema, as increased preload and afterload produced by inflation may worsen these conditions. Pregnant women should not have the abdominal compartment inflated because of risk to the fetus. Use of MAST with injuries or known bleeding sites above the diaphragm remains controversial because redistribution of blood flow to a nontamponaded area may lead to increased blood loss, while circulation to vital organs such as the heart and brain may be increased. Profound hypotension has been seen after rapid deflation of the antishock trousers, probably resulting from reactive vasodilatation in areas previously compressed. Deflation should always be gradual and well monitored, with only one compartment depressurized at a time. In the event of a dramatic fall in blood pressure during deflation, the suit should be reinflated appropriately and fluid infusion continued. If surgical treatment is indicated, deflation of the garment should take place in the operating room only after anesthesia is induced and the surgical team is prepared to operate.

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Overdose Update—Diminishing Drug Absorption

EMERGENCY PHYSICIANS have empirically used a variety of techniques to lessen gastrointestinal absorption of poisons; unfortunately, the efficacy of such techniques has not been subjected until recently to careful analysis. Newer studies should provide us with a more systematic and rational approach to poisoned patients.

General supportive care, combined with attention to and protection of the airway, remains the most critical aspect in the treatment of most cases of poisoning or overdose. Initial efforts at diminishing the total drug burden can be significantly valuable, however. Ipecac-induced emesis removes a greater amount of material than lavage and is preferable unless there is altered mental status or decreased gag reflex. Both are contraindicated in caustic ingestions, and may be inappropriate in hydrocarbon ingestion. Ipecac syrup is virtually nontoxic when used in standard doses. Its use is effective in 95 percent of patients, including those who have overdosed on antiemetics. There is no evidence that emesis is facilitated by having a patient drink large quantities of water; significant dilution may actually encourage greater absorption, as well as moving the drug into the small bowel where it is not amenable to either emesis or lavage. Carbonated beverages apparently do not diminish the effectiveness of ipecac, and in treating children may increase its palatability.

Activated charcoal has been shown in experimental overdose situations to significantly decrease drug con-

centrations and to favorably affect outcome. Charcoal should be used in virtually all overdose cases; most tested chemicals and drugs are adsorbed, and there are few contraindications. Charcoal should be avoided if it adsorbs an orally given antidote used in a specific poisoning. Adsorption of orally administered acetylcysteine by charcoal has been suggested in one study, but was seemingly absent in another. Until this is clarified activated charcoal should probably be withheld in major acetaminophen overdoses. Likewise, charcoal will adsorb orally administered ethanol, and thus should be withheld in methanol and ethylene glycol overdose.

Charcoal palatability can be increased by the addition of sorbitol or saccharin, the latter of which can be used in a 1:20 dilution and thus not increase total volume of charcoal that has to be swallowed.

Cathartics have not been proved to be beneficial in overdose cases, but recent studies show that at least in some cases they actually increase the adsorptive capacity of charcoal. Magnesium cathartics, in particular, increase cathartic removal of salicylates and several other substances.

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Coelenterate (Man-of-War) Envenomation

Recreational and industrial pursuits in coastal tropical waters have increased the number of envenomations inflicted by coelenterates (cnidarians) on humans. The most frequent offenders are *Physalia physalis,* the Atlantic Portuguese man-of-war, and *Physalia utriculus* (bluebottle), the Pacific version. These predators are free-swimming, pelagic organisms composed of a nitrogen and carbon monoxide-filled sail (pneumatophore) up to 30 cm long from which are suspended nematocyst (venom organelle)-laden tentacles. These tentacles may be numerous and measure up to 30 m (100 ft) in length *(P physalis).* When the animal moves in the ocean, these structures coil and fold to produce stinging "batteries," which may involve more than a million nematocyts.

Nematocyst venom includes toxic fractions that can invoke any and all of anaphylaxis, muscle spasm, exquisite pain and neurologic-cardiovascular collapse. Venom components include adenosinetriphosphatase, fibrinolysin, hyaluronidase, histamine, peripheral calcium antagonists, myocardial depressants, hemolysins and dermatonecrotic agents. Milder envenomation may provoke only an irritant dermatitis, whereas severe stings may induce generalized multisystem failure.

The immediate therapy for coelenterate stings is gentle topical application of isopropyl alcohol (40 percent) or acetic acid (5 percent). Fresh water or abrasion will discharge unexploded nematocysts and should be avoided. Following the initial detoxification, the remaining organelles can be removed by shaving the affected area. All patients should receive appropriate tetanus prophylaxis. Muscle spasm and pain are controlled with the administration of calcium gluconate and narcotics, respectively. Severe envenomations may require advanced life support. Washed-up tentacle fragments can retain activity for months. In children who ingest these, acute airway obstruction may develop from local oropharyngeal edema. Prompt detoxification and airway management is often lifesaving. Steroid administation has not been shown to be of definitive benefit.

There is not yet an effective antivenin for the sting of *Physalia,* as there is for *Chironex fleckeri* (box-jelly or sea wasp). The increased incidence of envenomations has provided impetus for a growing interest in the development of such an agent.

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Mechanism of Blood Flow During Cardiopulmonary Resuscitation

Cardiopulmonary resuscitation (CPR) is a therapeutic method that over the past 20 years has proved to be the critical first component in the management of sudden cardiac death. New concepts and controversies have recently been generated regarding the mechanism of blood flow during CPR: The central issue and major controversy is whether blood flow results from compression of the heart between the sternum and spine, as initially espoused by Kouwenhoven and colleagues, or whether antegrade flow is primarily due to the generalized rise in intrathoracic pressure that occurs during the act of chest compression, as suggested by animal and human investigations at Johns Hopkins University, the University of California, the Baylor College of Medicine and the University of Washington.

According to the latter theory, blood flow during CPR results from rhythmic increases in intrathoracic pressure during chest compression. The increase in intrathoracic pressure is transmitted directly to the extrathoracic arterial bed but, due to closure of venous valves, not to the peripheral venous system. A peripheral arterial-to-venous perfusion gradient is thus established that facilitates blood flow. This theory is supported by the finding that pressures in the cardiac chambers and ascending aorta rise to a level equal to the change in intrapleural pressure during chest compression. (If selective cardiac compression were to occur, ventricular pressures would exceed atrial pressures). In addition, cineangiographic studies in animals and two-dimensional echocardiographic studies in hu-

mans have shown that during CPR the left heart functions more as a passive conduit than as a pump. Implicit in the "chest pump" hypothesis for blood flow is that manipulations that increase intrathoracic pressure during CPR increase left heart outflow.

Regional perfusion studies using radiolabeled microspheres have shown a significant improvement in cerebral flow when simultaneous chest compression and lung inflation are used during CPR. However, simultaneous chest compression and lung inflation do not improve myocardial perfusion. In fact, coronary flow using conventional or newer methods of CPR averages only 1 percent to 3 percent of control flow!

Complications of newer CPR techniques in studies using animals appear to be minimal. Barotrauma from high airway pressures is infrequently noted and ventilation is more than adequate (provided a patient is intubated and positive pressure is used). The efficacy and safety of simultaneous chest compression and lung inflation in improving survival for victims of sudden death is being assessed in a Miami field study.

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Compelling Treatment After Suicide Attempts

A LARGE PROPORTION of the poisonings seen in emergency departments are actually the result of suicide attempts or suicide gestures. Patients frequently ingest a potentially lethal dose of a drug and then call for help. This seemingly paradoxical behavior may continue in the emergency department when the patient readily admits to a drug ingestion but refuses treatment. The attending physician is presented with an apparent legal and ethical dilemma: a patient who needs help yet refuses therapy.

The fundamental legal principle that people have the right to make major decisions about their bodies has long been recognized by the courts. In a 1914 decision Cardozo noted, "Every human being of adult years and sound mind has a right to determine what shall be done with his own body; and a surgeon who performs an operation without his patient's consent commits an assault for which he is liable in damages."

Some authors cite the 1960 case of *Natanson v Kline* as the first suit in the modern era of malpractice of a physician who failed to receive informed consent for treatment. During the 20 years since *Natanson,* the doctrine of informed consent has had a rapid evolution. Clearly a competent adult has a legal right to refuse treatment. Numerous cases show that this right extends to the refusal of potentially lifesaving therapy, except when another person or the state has a compelling interest in the patient's continued life. Legislation to permit persons to direct the conditions for their own terminal care has become commonplace, with nearly 100 different acts proposed or enacted in the United States by 1978.

Patients' rights notwithstanding, a drug overdose patient must be treated in an emergency department. Suicide has been defined as the intentional, voluntary, nonaccidental taking of one's own life. Where it has been shown that a person's refusal to submit to medical treatment is likely to result in death, which death may be classified as a suicide, the state may compel treatment. It has been argued that accepting a patient's refusal of treatment for a suicide attempt may be aiding in the suicide, thus leaving a physician criminally liable. The Lanterman-Petris-Short Act directs that any person who "is a danger to others or to himself, or gravely disabled" shall be placed in an approved "facility for 72-hour treatment and evaluation." Under the act, " 'Intensive treatment' consists of such hospital and other services as may be indicated."

We advise emergency physicians to obtain a signed informed consent when possible. However, all conditions that are an immediate threat to life or limb should be treated regardless of ability to obtain consent. This includes treating potentially life-threatening poisonings and overdoses. A psychiatric evaluation is a mandatory part of emergency treatment of drug overdose. The evaluation should be done as early as medically possible, and certainly before a patient is permitted to leave the emergency department. After a patient is in a stable condition and out of immediate danger from a delay in treatment, the physician should contact a probate court for directions on further, less urgent therapy.

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Overdose Update—Antidotes

SPECIFIC ANTIDOTES are unnecessary in almost all cases of overdose, but can be lifesaving in a few selected instances. A number of recently described or experimentally promising antidotes deserve mention.

Treatment with the oral administration of acetylcysteine in the United States, or intravenously given acetylcysteine and orally given methionine in Great Britain, has been shown to greatly diminish the incidence of significant hepatic necrosis following acetaminophen overdose. Effects on renal toxicity are not known. Patients found to have blood concentrations suggesting possible toxicity on standard acetaminophen nomography studies (which must be evaluated with regard to amount of time following drug ingestion) should be begun on a standard protocol of 18 doses of acetylcysteine.

Alkalinization of the serum to a pH of 7.50 to 7.55

seems to be the treatment of choice for severe hypotension or major dysrhythmias due to tricyclic antidepressant overdose. Bicarbonate therapy gives optimal results, but hyperventilation may also be effective. Phenytoin may well be another useful agent in this circumstance. It is theoretically advantageous because it does not increase atrioventricular block, and has been used successfully in one small series of mild overdoses. It has not yet been shown to work on patients with major overdose, however. Bicarbonate therapy to correct serum and cerebrospinal fluid acidosis, rather than to alkalinize the urine, is also extremely important in major salicylate overdose.

A number of other antidotes show significant promise. The use of pyridoxine may be critical in cases of significant isoniazid overdose, and folic acid may become a simple, safe, inexpensive and extraordinarily effective antidote for methanol and formaldehyde poisoning. Pyridoxine may work by preventing the decrease in brain γ-aminobutyric acid seen with isoniazid overdose; it has been associated with decreased incidence of seizures in small numbers of patients. Folate derivatives have been dramatically successful in experimental methanol and formaldehyde poisonings in animals. Formic acid produced by the metabolism of these drugs plays a major role in their toxicity, and folate significantly increases formate oxidation.

Naloxone hydrochloride, traditionally used for opiate overdoses, has been shown to have an effect on an increasing number of drugs. Of these, the most important is propoxyphene, for which naloxone should be given in doses about ten times those used for opiates. A variety of other agents, including ethanol and diazepam, have also been at least partially reversed in some experimental situations by the administration of naloxone, but the clinical significance of this is not clear.

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Hyperbaric Emergencies

ALTHOUGH THE USE OF increased atmospheric pressure to treat disease has a colorful (and at times inglorious) history that dates back to 17th century England, only in the past 20 years has a scientific basis for hyperbaric oxygen therapy been derived. Most physicians, however, remain unfamiliar with the principles of and legitimate indications for hyperbaric oxygen therapy (HBOT). Emergency physicians have a particular need to know about this therapy because many hyperbaric emergencies present via emergency departments.

Five mechanisms of action of hyperbaric oxygen therapy are currently recognized: (1) the mechanical effect of increased pressure, (2) the mass action effect of pure oxygen at increased pressure, (3) the vasoconstrictor effect of hyperbaric oxygen, (4) direct and indirect antibiotic effects and (5) enhancement of wound healing (applicable to compromised wounds only). In general, more than one of these effects are useful in a given condition. In no case does hyperbaric oxygen therapy supplant standard medical and surgical treatment; it is always adjunctive.

The Undersea Medical Society has issued a report on hyperbaric oxygen therapy that groups conditions that have been treated with hyperbaric oxygen into one of four categories according to the apparent efficacy of such treatment. Category I disorders are those for which hyperbaric oxygen therapy is the primary method of treatment (for example, decompression sickness and diving air embolism) or for which the efficacy of adjunctive hyperbaric oxygen therapy has been amply shown by research and clinical experience. Among the acute nondiving-related category I conditions are carbon monoxide poisoning, cyanide poisoning, smoke inhalation with presumptive carbon monoxide or cyanide poisoning, iatrogenic or traumatic air embolism, gas gangrene, mixed aerobic and anaerobic infections causing tissue necrosis, and cases of exceptional blood loss or life-threatening anemia when blood transfusion is impossible or delayed.

Category II disorders are those for which data from animal studies or from clinical experience indicate a beneficial role for adjunctive hyperbaric oxygen therapy but for which the data are limited. Emergency conditions included in category II are acute peripheral arterial insufficiency (due to any number of causes), crush injury, head and spinal cord trauma (but only if HBOT can be started within four hours of injury), retinal artery insufficiency and thermal burns. Some investigators have also found hyperbaric oxygen therapy to be a useful surgical adjunct in reimplantations, vascular and cardiac operations, scleral buckling procedures and surgical procedures in severely ill patients.

Category III disorders are those for which clinical data are very limited or only theoretical reasons suggest a possible beneficial role for hyperbaric oxygen therapy. HBOT must be viewed as investigational only in these conditions. Acute conditions included in category III are poisoning from hydrogen sulfide or carbon tetrachloride, ergotism, frostbite, musculoskeletal compartment syndromes, acute cerebrovascular accidents, migraine and cluster headaches, acute mesenteric thrombosis, sickle cell crisis and pneumatosis cystoides intestinalis.

Category IV disorders are ones for which there is no rational basis for using hyperbaric oxygen therapy. These include arthritis and other degenerative problems, hypertension and loss of hair color or sexual vitality. Regrettably, hyperbaric oxygen is occasionally being used to treat these kinds of conditions, but such practice should be strongly discouraged.

Hyperbaric oxygen therapy was once an exotic treatment confined to very few centers, but the development

of less expensive and less complicated monoplace hyperbaric chambers, increasing evidence of the benefits of this form of therapy and the expansion of the recreational and commercial diving industries have led to the proliferation of hyperbaric treatment facilities in recent years. Because many of the established indications for this treatment will be seen first in an emergency department, emergency and other acute care physicians should be familiar with the principles of hyperbaric medicine and should maintain a close liaison with local and regional hyperbaric treatment facilities.

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Naloxone—New Uses?

THE ENDOGENOUS OPIATE β-endorphin is stored in the anterior pituitary gland along with adrenocorticotropic hormone (ACTH), and in situations of acute stress both ACTH and β-endorphin are released. Endogenous opiates, like exogenous opiates, have been shown to produce hypotension and bradyarrhythmias; it has been suggested that endorphin release may contribute to the hypotension associated with a variety of shock states in humans.

Naloxone hydrochloride (Narcan) is a narcotic antagonist without independent agonist properties. It is approved by the Food and Drug Administration for treatment of narcotic drug overdose, narcotic depression of newborn infants and reversal of narcotic analgesia. Naloxone works by selectively competing with narcotic agonists for specific opiate receptor sites in the central nervous system. All the apparent physiologic effects of naloxone in a narcotized patient—mydriasis, piloerection, agitation, respiratory stimulation and hypertension—are due to reversal of narcotic effects. Naloxone has been proved to be extremely safe and effective for its approved uses. With the discoveries of β-endorphin, as well as β-enkephalin and specific opiate receptors in the central nervous system, and the observations regarding the physiologic effects of endorphin noted above, new applications for naloxone, particularly in shock states, have been considered.

In 1978 Holaday and Faden showed naloxone-mediated reversal of endotoxin-induced hypotension in rats. Similar salutary effects have been reported in a variety of experimental studies of hemorrhagic shock in animals. Naloxone treatment has also been shown to protect against shock in cats with spinal cord injury and is associated with improved neurologic recovery in these animals. Preliminary observations in patients with septic or cardiogenic shock refractory to conventional fluid and pressor therapy indicate that naloxone therapy can have a beneficial effect on systemic arterial pressure, cardiac output and mental status. Very large doses (up to 8 mg) have been used and the degree of improvement in blood pressure response has been highly variable. Although these studies are encouraging, they are preliminary in nature and the use of naloxone in shock remains entirely experimental.

Several anecdotal reports suggest a possible future role for naloxone administration in the reversal of alcohol- and diazepam-induced central nervous system depression, as well as correction of hypotension and apnea in clonidine poisoning. The mechanism of action is not established in these cases, but may again be related to reversal of a still undefined endorphin-mediated phenomenon.

The effectiveness of the use of naloxone in cases of clonidine overdose is provocative. Clonidine administration has been reported to be effective in treating symptoms of narcotic withdrawal, presumably by antagonizing specific autonomic effects. The usefulness of naloxone in treating clonidine overdose suggests that clonidine may itself stimulate endogenous β-endorphin production.

With naloxone, a drug that for the past ten years has been used with great effectiveness in a small number of clinical situations, we appear to be on the verge of a wide variety of valuable and exciting new applications. Further studies are needed to define appropriate doses, effects and possible complications.

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Poisoning With the New Antidepressant Maprotiline

MAPROTILINE HYDROCHLORIDE (LUDIOMIL) is a tetracyclic antidepressant now available in this country after extensive use in Europe. As its use and sales increase in this country, emergency physicians can expect to see more patients with maprotiline side effects and overdoses.

Maprotiline has a half-life of between 27 and 58 hours in normal volunteers given therapeutic doses. It is 88 percent protein bound and has an enormous apparent volume of distribution (22.6 liters per kg of body weight).

In therapeutic doses, side effects of drowsiness, dry mouth, hypotension, tachycardia and incomplete heart block occur with an incidence similar to those of the tricyclic antidepressants, but there is a pronounced increase in the incidence of seizures.

Maprotiline overdose also differs from overdose with tricyclic antidepressants in the incidence of drug-induced seizures. As many as 25 percent to 50 percent of adult patients overdosing on maprotiline have seizures, compared with a 6 percent incidence reported with tricyclic antidepressants. Other symptoms seen with maprotiline overdose in approximate order of frequency

include drowsiness, coma, respiratory depression, bradycardia, tachycardia, cardiac arrest, heart block, hypotension and hypertension. Several cases of fatal overdose with maprotiline (2 to 10 grams), either alone or in combination with other drugs, have been reported.

No specific antidote for maprotiline overdose exists. Induction of emesis or use of gastric lavage should begin as soon as possible after ingestion. Gastric instillation of activated charcoal and cathartics should further reduce absorption. Because up to 30 percent of absorbed maprotiline is excreted via the biliary system, prolonged gastric suction or repeated doses of activated charcoal will cause more rapid elimination of the drug. The large volume of distribution renders forced diuresis, dialysis and hemoperfusion ineffective. Systemic alkalinization by bicarbonate therapy or hyperventilation (or both), which has proved successful for cardiac arrhythmias and vascular collapse in tricyclic overdoses, has not been reported with maprotiline overdoses. Additional cardiovascular support, such as fluid replacement, pressor agents and heart pacing, is also indicated for refractory vascular collapse. Endotrachial intubation or mechanical ventilation are occasionally necessary. Seizures should be treated with the administration of diazepam or a barbiturate. The use of physostigmine for the treatment of cardiac arrhythmias or seizures is controversial in tricyclic antidepressant overdoses; although its use has been reported, caution is advocated in the use of physostigmine in maprotiline overdoses.

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Single-Dose Treatment of Urinary Tract Infections

SINGLE-DOSE TREATMENT of cystitis has been shown to be efficacious, inexpensive and relatively free of side effects when compared with conventional therapy. Among women, uncomplicated urinary tract infections are the most common of all bacterial infections, affecting an estimated 6 percent of the adult female population each year. In an additional 3 percent the acute urethral syndrome—that is, symptoms of cystitis without significant bacteria on culture—develops. Traditionally, uncomplicated cystitis has been treated with the administration of two to four doses a day of a variety of antimicrobial agents for a period of 7 to 14 days. Such therapy is effective in about 85 percent of patients and results in adverse reactions, including rash, vaginal candidiasis and gastrointestinal upset, in up to 30 percent of patients.

Recently a number of investigators have reported the efficacy of single-dose antibiotic regimens in the treatment of acute, uncomplicated urinary tract infections in women. Agents that have led to successful results include sulfadoxine, amoxicillin, kanamycin, sulfisoxazole and trimethoprim-sulfamethoxazole. The most widely used of these single-dose therapies is a single 3-gram dose of amoxicillin or a single dose of two double-strength trimethoprim-sulfamethoxazole tablets. In carefully controlled prospective studies the use of single-dose therapy is as efficacious as a standard ten-day course of antibiotics. The incidence of adverse reactions associated with single-dose therapy is significantly lower than with conventional therapy. In one study, clinically important side effects were observed in 4 percent of patients treated with single-dose and 24 percent of those with conventional therapy.

Women who are not candidates for single-dose therapy include those with diabetes mellitus; pregnancy; renal calculi, or upper urinary tract infection characterized by fever, chills and flank pain. (Children and men also are not candidates for single-dose therapy.) Failure of short-term therapy may indicate the presence of renal bacteria. In several studies the presence of antibody-coated bacteria in the urine has been a predictor of therapeutic failure in both short- and long-term therapy. However, the correlation between the presence of antibody-coated bacteria and upper urinary tract disease is not reliable.

Patients who are candidates for single-dose therapy should be instructed that they should expect their symptoms to resolve within 48 to 72 hours. If symptoms do not resolve, they should return for a repeat analysis of urine, as well as urine culture and sensitivity test. If a urine analysis shows pyuria and bacteriuria, the patient should receive conventional antimicrobial therapy for seven to ten days and be scheduled for a repeat urine culture about five days after termination of therapy. The results of the sensitivity test should be checked to insure that the antibiotic selected is appropriate. Resistance to the initial antibiotic given may explain the failure of single-dose therapy.

If a urine analysis shows pyuria and no bacteriuria or if the urine culture is negative, the patient probably suffers from an acute urethral syndrome; in this instance, the patient should be treated for ten days with tetracycline, 500 mg four times a day. Patients who have both a negative urine culture and normal findings on analysis of urine may have either gonococcal urethritis or nongonococcal acute urethral syndrome. The presence of the former may be diagnosed by a urethral culture for *Neisseria gonorrhoeae;* the latter may be diagnosed by culture of a urethral specimen for *Chlamydia trachomatis.*

In summary, single-dose antibiotic therapy should be considered for uncomplicated lower urinary tract infections in women. It appears to be as efficacious as conventional therapy and to be associated with significantly fewer adverse reactions. The failure of this

therapy suggests the presence of upper urinary tract infection and may be an indication for radiologic investigation of the urinary tract.

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Radiography in Cervical Spine Trauma

ONE OF THE MOST CHALLENGING and vexing problems in emergency medicine is cervical spine trauma. Not only do patients with such trauma often have multisystem injuries—in which abdominal and thoracic injuries may have the highest treatment priority—but they also may have an altered mental status from associated head injury or concomitant use of alcohol or drugs. Interpreting preliminary radiographs is often difficult because of the complex anatomy of the area and the technically suboptimal studies that sometimes result from portable technique, poor patient cooperation and reluctance to move a patient for proper positioning. Nonetheless, failure to recognize significant injury may result in disastrous consequences.

The traditional radiographic examination for suspected cervical spine trauma has been a cross-table lateral view. Although this is a generally quick and effective way to assess most significant injuries, some Jefferson and odontoid fractures, as well as rotary injuries of C1-2, may not be apparent on the cross-table lateral view, and injuries involving C-7 may be difficult to interpret because of overlapping soft tissues and bony structures of the shoulder. Occasionally, even mid-cervical injuries may be missed on a single cross-table lateral view because of the subtlety of the injury or poor technical quality of the initial radiographs. Consequently, a standard anteroposterior and open-mouth or modified odontoid view should be done routinely before mobilizing a patient's head or neck in all cases of suspected cervical spine injury. Likewise, vertebral arch views (pillar views) should be done if there is evidence of a hyperextension injury.

Although anteroposterior and lateral radiographs continue to be the mainstay of radiographic screening in spinal injuries, their use leads to an underestimation of the degree of injury in a substantial number of patients. In the past, plain film tomography has been used to further evaluate questionable findings seen on the initial radiographs; however, as with cranial and abdominal trauma, computerized tomography (CT) has added a new dimension to the management of spinal injuries.

CT studies can provide information about spinal injuries that may not be available from plain radiographs or conventional tomography, and they do this rapidly and safely. Most CT examinations of the cervical spine can be completed within 30 minutes, often in conjunction with studies of the head, chest or abdomen, and the only movement that is required is sliding a patient on and off a CT scanner couch. CT scans clearly delineate vertebral alignment and integrity, especially of the posterior elements. They are generally easier to interpret than conventional tomograms because of their superior contrast resolution, and they expose patients to less radiation. In addition, CT gives information about the neural canal (for example, the location of bone or bullet fragments and whether they compromise the canal), spinal cord, thecal sac and nerve roots. When available, sagittal and coronal reformatted images are useful in showing the state of the neural canal in the longitudinal dimension without requiring additional patient movement or radiation.

In a number of cases the method of treatment for a spinal injury has been changed directly as a result of CT findings. Thus, a CT scan of the cervical spine should be done whenever possible in the presence of a bony injury seen on preliminary radiographs or when a neurologic deficit appears to be from spinal cord injury, even in the absence of bony injury detectable on the initial radiographs.

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Hypertensive Emergencies

A PRONOUNCED AND SUDDEN RISE in blood pressure may represent an immediate threat to life. Prompt reduction of blood pressure in such settings is essential to prevent or reverse the morbid consequences.

The urgency of the clinical situation is determined by the presence or absence of acute end-organ dysfunction. Thus, patients with intracerebral hemorrhage or hypertensive encephalopathy, acute left ventricular failure or acute myocardial ischemia must have their blood pressure lowered immediately. Sodium nitroprusside is the drug of choice for such patients, as it provides both effective and titratable antihypertensive effect and the ability to discontinue the drug quickly if tissue perfusion is impaired.

Nitroprusside is administered by constant intravenous infusion at a dose of 0.5 to 8.0 μg per kg of body weight per minute. Practically, this may be achieved by mixing 50 mg of nitroprusside in a solution of 250 ml of 5 percent dextrose in water and beginning the infusion (for a 70-kg patient) at 5 microdrops a minute (5 ml an hour). The infusion rate is then in-

creased every few minutes until the desired antihypertensive effect is achieved (usually a diastolic pressure of 110 to 120 mm of mercury). Though nitroprusside is generally reliably effective, its powerful antihypertensive effect may result in hypotension and impaired organ perfusion. In patients treated with nitroprusside constant monitoring of blood pressure is required. Though this is optimally achieved with an intra-arterial catheter, patients may be effectively monitored for a short time in an emergency department with frequent auscultation of blood pressure. Because nitroprusside has a very short duration of action, untoward side effects will usually resolve promptly when the infusion rate is slowed.

Many patients present with pronounced, potentially dangerous elevations of blood pressure, but without acute life-threatening end-organ dysfunction. Examples would include patients with retinal hemorrhages without encephalopathy, a recent change in indices of renal function or an elevated blood pressure and nonspecific symptoms (headache, dizziness, epistaxis, malaise). In such patients a nitroprusside infusion with its potential complications may not be warranted. Recent studies indicate that there are several effective therapies that can be initiated in an emergency department and that rarely produce adverse effects:

- "Minidose" diazoxide, a 150-mg bolus given intravenously, repeated every five minutes as needed to reduce the diastolic pressure to 110 mm of mercury or less.
- Oral administration of clonidine hydrochloride, 0.2 mg initially, followed by 0.1 mg each hour until the desired antihypertensive effect is achieved or a total dose of 0.7 mg has been given.
- A slow intravenous infusion of diazoxide (30 mg per minute), continued until the desired blood pressure is reached.
- Nifedipine, 10 to 20 mg given sublingually.

Regardless of which regimen is used, a closely monitored inpatient or outpatient response to administration of conventional oral medicines is essential. The treatment of such patients does not end with control of the blood pressure, but with an investigation of the possible factors that might have contributed to the precipitous rise of the blood pressure.

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Editorials

A New Design for WJM

With this issue the journal enters its 10th year under the title The Western Journal of Medicine and its 81st year of continuous publication, under a succession of titles.

Much of The Western Journal of Medicine's physical appearance was inherited from its immediate predecessor, *California Medicine*. The Epitomes section, for example, has been graphically the same since its introduction 13 years ago. The layout and design for Case Reports was established 14 years ago. The journal's cover has followed the same basic single-column index format for 20 years. Moreover, other features, added at other times, have reflected the design styles of their particular periods.

In short, during the growth and improvement of the journal its graphics became increasingly inconsistent. In fact, it came to comprise so many different styles of headings and page layouts that one almost could have used an average issue to illustrate the recent history of medical journal design.

The Western Journal of Medicine now is the official scientific publication of seven western state medical associations. In addition, five western scientific societies have just affiliated with the journal. The circulation has reached some 47,000. With all of these factors in mind, the time seemed appropriate to take an objective look at the journal's appearance. This has been done and after some months of deliberation, development of design criteria and reviews of numerous design proposals, the results are embodied in the present issue. We hope our readers approve. —MSMW

Therapeutic Plasma Exchange: A Healthy Dose of Skepticism

An aphorism attributed to Sir William Osler asserts, "One should treat as many patients as possible with a new drug while it still has the power to heal." In the case of therapeutic plasma exchange, the medical community has embraced this tongue-in-cheek admonition with a singular enthusiasm. An estimated 50,000 therapeutic apheresis procedures were done in the United States in 1981 and about 3,000 more were carried out in Canada. Europe and Japan, with a head start in applying membrane and hollow fiber filtration techniques, seem determined to equal or surpass these figures. More than 50 different diseases have been treated by plasma exchange and future application seems to be limited only by patient availability and by physicians' imagination.

The term "plasmaphaeresis" was coined at the beginning of this century.[1] Its root is a Greek verb meaning to take away or withdraw and refers to the separation of plasma from whole blood with the return to the donor—originally dogs—of the sedimented blood cells in a resuspending medium. Early human applications involved the manual removal of plasma that contained paraproteins from patients suffering the effects of hyperviscosity from macroglobulinemia. When small amounts of plasma were removed and replaced with crystalloid solutions, plasma viscosity could be lowered significantly. No controlled trials were required to show clinical improvement.

The current therapeutic procedure, more accurately called "partial plasma exchange," or "plasma exchange" for short, is the by-product of a technology developed for an entirely different purpose. Blood cell separators were originally designed to collect large numbers of platelets and granulocytes from normal blood donors for transfusion. These instruments proved capable of exchanging liter volumes of plasma and therefore of depleting the circulation of numerous soluble factors, including immunoglobulins, lipoproteins, immune complexes and metabolic intermediates associated with a variety of disease processes. A 3- to 4-liter plasma exchange is now a technically uncomplicated procedure. It can be repeated several times a week if necessary and, depending on the rates of synthesis and degradation, can rapidly reduce the particular plasma constituent up to 70 percent.

The major questions relating to therapeutic plasma exchange remain scientific ones; these are the same questions posed by Robert Burton[2] more than 300 years ago: "In letting of blood three main circumstances are to be considered, 'who, how much, when.'" In considering the "who," one should also ask whether plasma exchange modifies the course of the underlying disease, provides only symptomatic relief, is merely a mechanical placebo or, in fact, causes some degree of harm. Even when the procedure is of proved effectiveness, physician and patient must weigh the degree of benefit against the rigors of the therapy. Does a modest decrease in morning stiffness justify semiweekly plasma exchange with the attendant risks, discomforts and expense?

Little evidence supports a role for plasma exchange as the primary form of therapy for any disease. Despite the recent spate of enthusiastic reports, there is a surprising consensus among experts that plasma

exchange represents adjunctive therapy for a select number of disorders; the indications for exchange and the supporting evidence are well summarized in the review article in this issue. The major medical controversies involve the following: (1) potential applications of plasma exchange to a wider range of conditions, especially for disorders where the pathophysiology is obscure and conventional therapy is either suboptimal or ineffective, and (2) the degree to which rigorous clinical trials are necessary to establish clinical efficacy.

The "how much" and "when" of plasma exchange are intimately related to the rationale for undertaking therapy. When a causative agent is recognized, for example, the paraprotein in macroglobulinemia, a therapeutic regimen can be designed to reduce it to an acceptable concentration. Still, variables such as concomitant drug therapy and the nature of the replacement solution may alter the synthesis, catabolism and distribution of plasma substances and may be critical determinants of the volume and frequency of treatment. These aspects of plasma exchange therapy have not been well studied. In diseases of unknown origin, objective therapeutic guides are rarely available. Yet depletions of complement components, rheumatoid factor and immune complexes, among other substances, are commonly cited as evidence that plasma exchange is effective therapy. Such substances may have no obvious relation to the cause or activity of the disease and their measurement is more appropriate for establishing machine efficiency than for determining the effectiveness of therapy.

When laboratory determinants of disease response are not available, physicians must depend on their clinical impressions of therapeutic effectiveness, notoriously unreliable in diseases of relapsing and remitting nature, especially in a small series of patients. Whereas large, randomized, prospective trials were not necessary to show the value of the use of plasmapheresis in macroglobulinemia, penicillin in pneumoccocal pneumonia or insulin in diabetes mellitus, these examples represent the exceptions rather than the rule. A 30 percent to 40 percent placebo effect is associated with most new therapies.[3] Foulds[4] reported that 80 percent of the uncontrolled trials in the literature show any given treatment to be effective, whereas only 25 percent of the randomized, controlled trials find the same treatment to be beneficial. Strikingly similar is a recent comparison of historical controls with randomized controls in six different therapies; 79 percent of the trials with historical controls reported therapy superior to control, whereas only 20 percent of randomized control trials could show efficacy.[5]

Such studies underline the unconscious bias that may distort a trial and emphasize how critical are careful selection and management of control groups in determining the outcome of a given clinical trial. In the case of plasma exchange, this may involve large, expensive, controlled clinical trials with "sham" treatment groups. Despite heated controversy, the National Institutes of Health and several university centers have adopted this approach as the most reasonable way to determine the true value of therapeutic plasma exchange. The Canadian government has established the Canadian National Plasma Exchange Study Group to conduct prospective controlled trials and will likely establish national therapeutic guidelines based on the outcome of these studies. Third-party insurers, among others, will be watching these studies with great interest.

Financial concerns have surfaced within the medical community, the federal government, private insurers and various consumer groups. While the economic issues are significant, it is likely that technology can substantially reduce the costs of plasma exchange should the scientific results provide the impetus to do so. Currently, in addition to personnel time, a plasma exchange involves the use of a $30,000 instrument and several hundred dollars' worth of disposable plastic supplies and replacement fluids. When procedure fees, professional fees, pharmacy fees and laboratory fees are totaled, the cost per procedure frequently exceeds $1,000. Reimbursement is sometimes contingent on being admitted to hospital for treatment, so that unnecessary hospital costs may be generated as well. On the brighter side, a new generation of instruments, specifically designed for plasma exchange, has been introduced. Based on filtration techniques, these instruments can potentially remove a more selective fraction of plasma and obviate the need for expensive replacement fluids. Even more specific are a variety of affinity columns already under evaluation in selected clinical situations. Once the principles of effective therapeutic exchange are better understood, the cost per procedure should drop substantially.

Whereas the list of potential complications is extensive, the risks of plasma exchange are small. Most adverse reactions are mild and related to allergies or volume changes. When plasma is used as a replacement fluid, the further risk of transfusion-transmitted diseases is introduced. Yet only 35 deaths associated with therapeutic apheresis have been discovered in a recent worldwide survey and several of these were more likely coincidental than causally related to the procedure. Although accurate figures for the number of procedures done in the same period are not available, when plasma exchange is carried out by experienced personnel, the mortality must be vanishingly small.

Therapeutic plasma exchange remains primarily an investigational procedure. The preliminary animal experiments of Abel and associates moved them to write:

> If this method can be employed without harmful consequences, it is probable that it could be applied in a bolder manner and in a greater variety of morbid states than the time honored but often debatable venesection of medical practice. An empirical method so universally practiced since prehippocratic days almost certainly contains a basis of truth.[1]

Enthusiasts tout the virtues of plasma exchange in an increasingly bold manner. Until the "basis of truth"

has been properly tested and established, it seems prudent to approach these claims with a healthy scientific skepticism.

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The Physicians' Share of Limited Dollars for Health Care

IT IS INCREASINGLY EVIDENT that the era of virtually unlimited dollars for health care has ended. Now and for the foreseeable future the number of dollars and other resources available for health care will be limited, actually quite finite instead of essentially infinite. The problems that this will pose have yet to be fully addressed. Physicians may reasonably be concerned with what might be their appropriate share of these limited health care dollars.

Victor Fuchs has considered this problem.[1] He points out that if the dollars for health care are limited the physicians' share of these dollars must bear some relationship to the nonphysician expenditures for health care. Quite simply the greater the nonphysician expenditures, the fewer dollars are available to pay for physicians' services. If this is true, it is clearly in the economic self-interest of physicians to work toward cost containment in the total expenditures for health care. And it would seem to call for something more than the Voluntary Effort (VE) which has produced some results but nowhere nearly enough.

What is to be done? Two approaches, one new and one not so new, seem necessary. First, physicians' fees or other compensation should be adequate and also clearly justifiable in terms of the economic value of the services rendered. Relatively little attention or study has been given to this. Some improvements are clearly needed. The thinking, problem solving or rendering of professional opinions or advice are not now compensated adequately in terms of their real economic value in health care. The American Society of Internal Medicine (ASIM) calls these "cognitive services" and recognizes that they are rendered by physicians in all specialties. ASIM believes that more incentives for greater use of these cognitive services are needed and that more equitable compensation for them could result in substantial savings in the overall cost of care. Benson Roe has called attention to the need for a more equitable distribution of physicians' fee dollars within the profession.[2] He believes that many surgical fees are unjustifiable especially when they remain high long after a procedure becomes routine or even commonplace. And in another dimension one may ask how justifiable is the substantial compensation above overhead costs that many physicians receive when machines or other health personnel do most of the work for which they are compensated. If physicians' fees or other types of compensation are to be perceived as both adequate and justifiable, the medical profession should address—and where necessary resolve—these sorts of issue, or risk losing control of its finances and perhaps of its destiny.

A second approach that seems necessary is to reassert and strengthen the central role of physicians and of the medical profession in health care in both medical and economic terms—that is, in assuring both quality and economic efficiency in health care. As Fuchs suggests this may not be easy and will require understanding and some compromise in working with administrators and other elements of the health care enterprise, if serious conflicts are to be avoided. However, if his basic premise is correct it is clearly in physicians' own economic self-interest, as well as in the interest of the public, to work in every way possible to restrain the nonphysician portion of health care expenditures whether for hospital care, drugs, administration or whatever.

It is significant, and even a happy prospect for genuine collaboration, that the actual economic self-interest of the great body of physicians seems to coincide so closely with the interests of those in government, business and elsewhere who are seeking ways to hold down the rate of growth of health care expenditures. From all this it is clear that arbitrary reductions in physicians' fees will never accomplish this goal (rather, this is likely to be counterproductive), nor is bureaucratic control of medical practice by administrators in or out of government a likely solution. Rather it is time for physicians and the medical profession to put their own economic house in order and also to reassert and strengthen their central role in patient care and at all other levels of health care, and to take the initiative to assure both quality and economic efficiency in all aspects of care. As Fuchs points out, to do this is in the economic self-interest of both the public and the profession.

—MSMW

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Case Reports

Severe Hypoglycemia Associated With Disopyramide

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DISOPYRAMIDE PHOSPHATE (NORPACE) has been widely used in the United States in recent years. It is a structurally unique antiarrhythmic agent with pharmacologic properties similar to quinidine.[1] Most adverse effects of disopyramide are attributable to its anticholinergic action, but recently uncommon but serious cardiac toxicities that include heart failure and an atypical ventricular tachycardia have been reported.[2,3] Goldberg and co-workers[4] recently described a case in which hypoglycemia developed in a patient following disopyramide treatment. We report two additional cases in which the use of disopyramide is associated with severe hypoglycemia and lactic acidosis.

Reports of Cases

CASE 1. A 74-year-old man was admitted to the University of Wisconsin Hospital (Madison) in October 1977 following a syncopal episode. He was first admitted to hospital in September 1974 in severe congestive heart failure when digoxin and diuretic therapy was instituted. He was readmitted in October 1976 for evaluation of recurrent syncopal episodes. A Holter monitor recording showed periods of sinus bradycardia, frequent runs of ventricular tachycardia and a brief period of slow idioventricular rhythm of 34 beats per minute. A demand pacemaker was implanted in October 1976 and quinidine sulfate therapy was started. The patient did well until September 1977, when he was admitted with congestive heart failure. He improved on treatment and was discharged on a regimen of procainamide hydrochloride, spironolactone, digoxin, furosemide and hydralazine hydrochloride.

At the time of admission in October 1977, he stated he had no chest pain, palpitations, dyspnea, orthopnea or paroxysmal nocturnal dyspnea. On physical examination he had a blood pressure of 100/60 mm of mercury and pulse rate of 72 beats per minute; scattered bilateral rales were heard over the lung bases. A chest x-ray study showed cardiomegaly, a right pleural effusion and the pacemaker electrode in the right ventricular apex. An electrocardiogram showed that he had a normally functioning pacemaker. Admission laboratory tests gave normal values.

A 24-hour Holter monitor recorded the presence of frequent premature ventricular contractions and short runs of ventricular tachycardia. The patient had received 500 mg of procainamide orally at midnight, 6 AM and noon on the day of admission. Procainamide (1 gram) was given at 6 PM. Shortly after midnight on day 2, he received 450 mg of disopyramide orally. At 1:30 AM the patient was noted to be hypotensive (systolic blood pressure was 54 mm of mercury); he then had a seizure. An intravenous infusion of metaraminol bitartrate solution was started and the blood pressure became stable. Within an hour the patient was conscious and responsive. The metaraminol infusion was discontinued and his hemodynamic state continued to be stable. At 8:30 AM the patient again became acutely hypotensive and an infusion of metaraminol solution was restarted, again stabilizing the blood pressure. He was alert and oriented. At 10:15 AM he had a generalized seizure and cardiopulmonary arrest. He was successfully resuscitated and use of a respirator was begun. Tests of blood specimens drawn at 8:36 AM showed a blood glucose level of 9 mg per dl. Immediately after the arrest, the blood glucose level was 47 mg per dl and 50 grams of dextrose solution was given intravenously. The electrocardiogram showed widened QRS and prolonged QT-U with giant U waves and a rate of 80 beats per minute before returning to a paced rhythm.

Pertinent and abnormal laboratory values are given in Table 1. Noteworthy are persistently low blood glucose and high lactate levels.

The blood pressure remained low despite therapy with direct-acting pressor agents; initially, dopamine hydrochloride and later norepinephrine (levarterenol) bitartrate were administered in combination with sodium nitroprusside. At least three 50-ml boluses of 50 percent dextrose solution were given during the next 24 hours. On day 3 at 9:15 PM he was found pulseless and was pronounced dead.

CASE 2. A 58-year-old man was admitted to William

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TABLE 1.—*Laboratory Values in Case 1*

Day and Time	*Serum Glucose mg/dl (N = 70-100)*	*Serum Potassium mEq/liter (N = 3.8-5.0)*	*Blood Po_2 mm/Hg (N = 95-100)*	*Serum pH (N = 7.35-7.45)*	*Serum Lactate mEq/liter (N = 0.2-1.2)*	*Comments*
Day 1	108	5.2	...	...	...	Procainamide, 500 mg given by mouth × 3 doses, and 1 gram at 6 PM*
Day 2						
8:36 AM	9	4.4	...	...	...	Disopyramide, 450 mg given by mouth shortly after midnight; 1:30 AM patient hypotensive and had a seizure; 8:30 AM patient hypotensive
10:15 AM	47	4.8	55	7.12	9.6	Generalized seizure and cardiopulmonary arrest; 50 percent dextrose in water solution given
12:00 PM	322	...	109	7.38	11.4	Blood pressure remained low despite dopamine and norepinephrine given in combination with nitroprusside. A bolus of 50 percent dextrose in water given throughout the next 24 hours
5:20 PM	79	...	126	7.52	3.1	
10:00 PM	149	5.2	...	...	...	
Day 3						
3:00 AM	51	5.2	...	...	12.3	
7:30 AM	51	5.8	...	...	...	
8:00 AM	43	...	...	...	...	
9:00 AM	...	...	...	...	12.9	
11:46 AM	86	5.5	94	7.42	17.2	
3:00 PM	56	...	...	...	10.6	
9:15 PM	...	...	...	...	...	Pronounced dead

*The patient's serum creatinine level on admission was 2.7 mg/dl and had risen to 5.3 mg/dl on the morning of day 3.

S. Middleton Memorial Veterans Administration Hospital (Madison) in May 1979 with a history of recurrent ventricular tachycardia. Four years before admission, a Bjork-Shiley aortic valve was implanted for calcific aortic stenosis, which was complicated by an intraoperative myocardial infarction. Postoperatively, he had mitral regurgitation and congestive heart failure. Ventricular arrhythmias developed and multiple antiarrhythmic drugs had been given in an attempt to control his ventricular arrhythmia, with limited success.

On admission he gave a history of a recent increase in symptoms of ventricular tachycardia, including palpitations, lightheadedness and weakness. Medicines being taken at the time of admission were quinidine, propranolol hydrochloride, warfarin, furosemide, potassium chloride, nitroglycerin, digoxin and diazepam.

On physical examination he was noted to be thin and pale and had a blood pressure of 110/80 mm of mercury, a pulse rate of 84 beats per minute and 18 respirations per minute. The prosthetic valve sounds were normal.

Admitting laboratory studies showed a low hematocrit level, a prolonged prothrombin time and serum electrolyte values within normal limits. An electrocardiogram showed a first-degree AV block and a nonspecific intraventricular conduction defect. The quinidine therapy was discontinued and disopyramide, 200 mg, was given by mouth every six hours starting on the first hospital day. The propranolol dosage was increased to 20 mg given every six hours. Serum disopyramide concentration 48 hours after the first dose showed a peak of 2.6 μg per ml and a trough of 1.8 μg per ml. On the third hospital day, an episode of ventricular tachycardia occurred and was terminated with the intravenous administration of lidocaine hydrochloride. On the tenth hospital day, he had abdominal pain and his extremities were cold. He vomited and was found to be pale, diaphoretic and having labored respirations. He was hypotensive with a palpable systolic blood pressure of 70 mm of mercury. An electrocardiogram showed a widened QRS and prolonged PR and QT intervals. He then had a cardiopulmonary arrest and resuscitation was initiated. Calcium gluconate and sodium bicarbonate were administered and the electrocardiogram abnormalities corrected.

The pertinent laboratory findings are listed in Table 2. The very low serum glucose and high serum potassium and lactate levels are striking. A glucose solution was given intravenously and administration of the disopyramide and propranolol was discontinued. The patient recovered but was lost to follow-up.

Discussion

Two cases of severe hypoglycemia occurred in patients who had received disopyramide. In both instances, the patients' serum glucose level was less than 10 mg per dl and was associated with hypotension and lactic acidosis. The first patient had a severe reaction within 90 minutes after administration of a single dose of disopyramide, though hypoglycemia was not reported until eight hours later. The sequence of events and available laboratory findings obtained after a second hypotensive episode and seizure strongly suggest they were related to hypoglycemia.

In the second case, the temporal relationship of hypoglycemia and disopyramide is not as clear. The

TABLE 2.—*Laboratory Values in Case 2*

Day and Time	Serum Glucose mg/dl (N=70-100)	Serum Potassium mEq/liter (N=3.8-5.0)	Serum pH (N=7.35-7.45)	Serum Lactate mEq/liter (N=0.2-1.2)	Plasma Bicarbonate mEq/liter (N=21-28)	Comments
Day 1	112	3.6	...	...	22	Disopyramide, 200 mg given by mouth every 6 h; propranolol, 20 mg, given by mouth every 6 h; continue warfarin, furosemide, potassium chloride, digoxin and diazepam administration
Day 10						
8:00 AM	113	5.4	...	...	18	
10:00 AM	...	6.5	7.20	...	<8	Pale, diaphoretic, hypotensive; transferred to coronary care unit
11:00 AM	...	...	...	12.3	...	
12:00 PM ..... (immediately after arrest)	4	8.5	...	12.1	...	Cardiopulmonary arrest; calcium gluconate and sodium bicarbonate given
2:00 PM	5	6.6	...	...	...	Dextrose, 50 percent in water, given

patient had a normal serum glucose level earlier that day. He had been taking disopyramide for ten days without prior evidence of hypoglycemia.

In a recent review of drug-induced hypoglycemia, Seltzer[5] notes several predisposing factors. These include restricted carbohydrate intake, increasing age, alcohol intake and abnormal liver or renal function. The second patient was receiving propranolol concurrently with the disopyramide and had recently had his propranolol dose increased. Propranolol has been reported to cause hypoglycemia.[6-9] This may have contributed to the severity of his hypoglycemia but because he had been receiving propranolol for over a year before this incident, it is not likely to have been the sole cause.

The relationship between hypoglycemia and lactic acidosis is not clear in these patients. Lactic acidosis can be due to inadequate tissue perfusion with increased production of lactate or a reduction in hepatic lactate extraction (or both).[10] Both patients were hypotensive before blood specimens were drawn.

Disopyramide has been reported to cause significant myocardial depression.[2,11] Perhaps disopyramide decreased cardiac output in these patients by decreasing contractility or by causing an atypical ventricular tachycardia that resulted in inadequate tissue perfusion. Hypoglycemia may occur as a consequence of reduced hepatic blood flow, though this is uncommon.[12]

The first patient was noted to have a generalized seizure, which can also be a cause of lactic acidosis.[10] If there were a defect in hepatic lactate uptake this could result in both lactic acidosis and hypoglycemia due to a decrease in a gluconeogenic substrate.[10]

Medalle and associates[13] reported three cases of lactic acidosis and hypoglycemia; in one of these the lactic acidosis resolved with the administration of glucose alone. They felt that hypoglycemia in the presence of hepatic damage could impair the hepatic uptake of glucose precursors including lactate, which would then lead to decreased gluconeogenesis and increased hypoglycemia.

Whether the hypoglycemia or the lactic acidosis occurred first remains speculative. In neither case was disopyramide toxicity or idiosyncrasy suggested at the time hypoglycemia was found. There have been more than 30 cases of hypoglycemia associated with disopyramide therapy reported to the manufacturer, most of the patients being asymptomatic with glucose levels ranging from 50 to 60 mg per dl (E. N. Shubert, PhD, Searle Laboratories, oral communication, July 15, 1980). In addition, pilot studies in animals and humans have shown a trend for glucose lowering by disopyramide. The mechanism of action is unknown.

Goldberg and colleagues[4] reinduced hypoglycemia in their patient with administration of disopyramide. The precise mechanism was not determined but disopyramide did not cause an increase in insulin release or a suppression of glucagon, whereas the glucose levels fell. The incidence of symptomatic hypoglycemic reactions to disopyramide appears to be low but clinically important and, in unusual circumstances, perhaps life threatening. Further controlled studies are needed to fully assess the mechanism of action and predisposing factors for such an effect.

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Diazepam Withdrawal

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BENZODIAZEPINES ARE AMONG the most widely used pharmacologic agents in the United States,[1] and diazepam is the most commonly prescribed.[2] True addiction to diazepam is believed to be unusual.[3-5] Withdrawal reactions to diazepam are uncommon but have been described.[6-33] We report the case of a patient who had withdrawal reactions on two separate occasions and we review the English language literature on this subject.

Report of a Case

A 40-year-old nonalcoholic woman with a history of bilateral nephrectomies and being maintained on hemodialysis was admitted to hospital for abdominal pain in 1978. A surgical procedure was carried out on the second day for a ruptured abdominal aortic aneurysm. Four days after the operation she became agitated, confused and combative, screaming and waving her arms periodically. She refused to talk to anybody, but when she was communicative, she expressed fears of being hurt. She was observed talking to imagined companions. There was no improvement after routine hemodialysis. Initial treatment with haloperidol, 10 mg given orally, resulted in some improvement within six hours, and haloperidol, 2 mg taken orally every eight hours, was prescribed. The next day she became visibly tremulous. The tremor was involuntary, symmetric, mostly distal and more severe in the upper extremities. She was also noted to grimace. The tremor was intermittent, with seconds to minutes between contractions. Diphenhydramine hydrochloride, 25 mg, was given intramuscularly every four hours, which resulted in only slight relief of symptoms. By the ninth postoperative day her tremors had significantly worsened. Treatment with diphenhydramine and benztropine mesylate administered intravenously was ineffective. Intravenous administration of 5 mg of diazepam resulted in a dramatic abatement of her tremors within 30 seconds. Treatment with diazepam, 5 mg taken orally every six hours, was continued and she showed progressive improvement. Subsequently the patient related a history of having taken diazepam, 5 to 15 mg a day, for the past seven years for anxiety.

In 1980 the patient was admitted to hospital for abdominal pain and partial small bowel obstruction. She was treated with nasal gastric suction, which relieved her symptoms. Diazepam therapy was discontinued. On the third hospital day severe tremors developed, with intermittent, involuntary jerking and twitching of the muscles of her face and extremities. The contractions were mostly distal, affecting mainly the upper extremities. There was no confusion, delirium or hallucinations. Her reflexes, plantar responses and sensory examination findings were normal, as well as her vital signs. The blood urea nitrogen level was 79 mg per dl and creatinine concentration was 18.5 mg per dl, unchanged compared with her usual predialysis baseline. Serum calcium, magnesium and electrolyte levels were within normal limits. Administration of diazepam, 5 mg orally every six hours, was reinstituted. Within 24 hours her symptoms of tremors and myoclonic jerks completely resolved.

Discussion

Diazepam withdrawal reaction was first described by Hollister and co-workers in 1963[28] in studies of diazepam treatment in newly admitted schizophrenic patients. We have identified 33 cases of diazepam withdrawal detailed in the English medical literature (Table 1).[6-27] The single most convincing case was reported by Winokur and associates,[26] with verification of the diagnosis by a placebo-controlled, double-blind protocol.

The exact incidence of diazepam withdrawal reactions is not known. In addition to the 33 cases noted above, several authors have reported in a general way cases of withdrawal reactions among their patients.[28-33] One possible reason why such withdrawal reactions are uncommonly seen is that patients may abort these reactions early on. They may think that their original symptoms are returning and reinstitute taking the drug.[4]

In the 33 reported cases,[6-27] the ages of the patients ranged from 21 to 72 years; 16 were women and 17 were men. The daily diazepam intake ranged from 15 mg to 500 mg a day. The duration of diazepam use before the onset of withdrawal symptoms ranged from ten days to ten years. In all of the patients withdrawal symptoms developed within 1 to 11 days after use of the drug was discontinued. Most of the patients were taking the diazepam for anxiety or neurosis.

Discontinuation of diazepam use was the result of a physician's attempt to detoxify a patient[16,21,25] or change the medication.[13] The history of diazepam use was known in some cases[7,9,19,24] but not in others.[8,22,23] Situations that required that nothing be taken by mouth, such as bowel or other surgical interventions, were frequently associated events.[16,26] Less common circumstances included treatment for tetanus[14] or overdose with benzodiazepines.[20] Additionally, use of the drug was discontinued or the dosage reduced by patients voluntarily[20,26,27] or involuntarily,[12,17] or there was a change in the work environment.[18]

A spectrum of signs and symptoms was seen in the reported cases.[6-27] They ranged from affective disorders with psychosis, confusion, agitation, hallucinations and delirium to motor dysfunctions with restlessness, trem-

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TABLE 1.—*Summary of 33 Cases of Diazepam Withdrawal Described in the English Literature*

Author	Age	No. of Patients	Diazepam Therapy			Associated Conditions	Onset of Withdrawal	Signs and Symptoms of Withdrawal
			Sex	Dosage mg/d	Duration			
Aivazian, 1964[6]	..	1	♀	30	Months	.....	Hours	Grand mal seizures
Barten, 1965[7]	52	1	♀	20	3 mo	Depression	3 d	Paranoid delusions, disorientation, tremulousness, agitation, hostility, restlessness, grand mal seizure
Relkin, 1966[8]	21	1	♂	40-60	10 d	Dystonia, musculorum deformans	1 d	Tremor, diaphoresis, tachycardia, fever, death
Gordon, 1967[9]	23	1	♀	60	1 yr	Anxiety	Days	Agitation, tremulousness, hyperhydrosis, dry mouth
Clare, 1971[10]	39	1	♀	90-500	6 yr	Disturbed sleep	Daily symptoms	Morning shakes, slurred speech, gross ataxia, withdrawal fits
Kendall and Clarke, 1972[11]	72	1	♀	70	1 mo	Tetanus	12 d of coma	Coma for 12 days
Woody et al, 1975[12]	25-26-	2	♂	100-150	2-3 wk	Heroin addict taking methadone hydrochloride	2-8 d	Anxiety, insomnia, tremor, grand mal seizures, tenseness, dizziness
Bant, 1975[13]	..	2	♀	30	2 yr	Anxiety, obsessive compulsive neurosis	2 d	Shaking, inability to stand
Malatinsky et al, 1975[14]	60-66	2	♂	80-120	11-34 d	Tetanus	11 d	Visual hallucinations, confusion, disorientation, memory deficits, emotional instability, irritability, motor restlessness, negativism, mutism
Vyas and Carney, 1975[15]	..	1	♀	30	3 yr	Anxiety	2 d	Grand mal seizures, confusion
Floyd and Murphy, 1976[16]	47-64	1 4	♀ ♂	20-40	5 mo-years	Depression	3-6 d	Disorientation, visual hallucinations, stubbornness, confusion, forgetfulness, irrational behavior, jitters
Fruensgaard, 1976[17]	46-74	3	♀	5-30	2 mo-years	Tenseness, headache, depression, hysterical neurosis	2-5 d	Confusion, agitation, delirium, perspiring, frequently laughing, widely gesticulating, jabbering, paranoid tendencies, hallucinations, incoherent speech
Rifkin et al, 1976[18]	23	1	♂	30	3 mo	Anxiety	5 d	Grand mal seizures
Dysken and Chan, 1977[19]	49	1	♂	15-30	7 yr	Anxiety, hyperventilation	7 d	Suspicion, confusion, disorientation, incoherence, loose association
Preskorn and Denner, 1977[20]	34-56	1 2	♀ ♂	40-100	6 mo-2 yr	Anxiety, insomnia, cardiac neurosis, nervousness, anorexia	3-5 d	Insomnia, anxiety, restlessness, grandiose delusions, confusion, disorientation, auditory and visual hallucinations, seizures, agitation, hostility, paranoid delusions
Agrawal, 1978[21]	30	1	♀	20-140	5 mo	Backache	5 d	Tremulousness, irritability, increased psychomotor activity, muscle cramps, photophobia, retroorbital pain, insomnia, visual hallucinations, paranoia, ataxia
Minter and Murray, 1978[22]	30	1	♂	20	Years	.....	2-3 d	Auditory and visual hallucinations, confusion, agitation, disorientation, delusions
Pevnick et al, 1978[23]	37	1	♂	30-45	1½ yr	Anxiety	9 d	Tremor, muscle twitches, cramps, facial numbness, dysphonia
deBard, 1979[24]	56	1	♂	40-80	10 yr	.....	10 d	Visual hallucinations, coma, grand mal seizures, disorientation
Miller and Nulsen, 1979[25]	37	1	♀	60-80	8 yr	Hyperventilation	12 d	Diarrhea, restlessness, anxiety, emotional lability
Winokur et al, 1980[26]	32	1	♂	15	6 yr	Anxiety	Few days	Anxiety, vertigo, tinnitus, blurred vision, generalized shakiness
Abernethy et al, 1981[27]	31	1	♀	100-120	2 yr	.....	2 d	Agitation, tremulousness, weakness

ors, myoclonic jerks and grand mal seizures. Some patients manifested the entire spectrum,* whereas in others only the psychosis developed[16,17,19,22] or the motor dysfunctions.[6,10,13,18,23] There were rare cases of coma[11,24] or death.[8]

Our patient had been taking 5 to 15 mg of diazepam a day for at least seven years when the withdrawal reactions developed. Within three to four days after diazepam intake was discontinued her symptoms became evident. The diazepam was initially prescribed for anxiety. Her clinical course clearly showed that there are two distinct components to diazepam withdrawal, and the treatment of each may differ. During the first episode, her initial presentation was an affective disorder with psychosis, confusion, paranoid feelings and delirium. Haloperidol administration was effective in controlling these symptoms, but then the motor dysfunctions became evident. During the second episode, there was no affective disorder and her only symptom was the myoclonic jerks. Resumption of diazepam therapy resulted in dramatic resolution of the motor dysfunctions on both occasions. We therefore diagnosed diazepam withdrawal in our patient based on the criteria proposed by Eddy and colleagues.[34] They state that

> the withdrawal or abstinence syndromes are made up of specific arrays of symptoms and signs of psychic and physical nature that are characteristic for each drug type. These conditions are relieved by readministration of the same drug or another drug of similar pharmacological action within the same generic type.[34]

The physiologic mechanism responsible for the affective and the motor dysfunctions of diazepam withdrawal has yet to be determined. The long duration of action and the presence of pharmacologically active metabolites probably explain why symptoms of diazepam withdrawal generally do not appear until several days after discontinuing use of the drug.[3] The interaction of benzodiazepine receptors in the brain with γ-aminobutyric acid (GABA) receptors may be important in the pathogenesis of the withdrawal reactions.[35-38]

The most effective treatment of diazepam withdrawal reactions is to resume taking diazepam. Intramuscular or intravenous administration of diazepam in a dosage of 5 mg results in rapid improvement.[13,17,19,24] Orally given diazepam in a dosage of 10 to 60 mg a day requires a longer duration for relief of symptoms, sometimes up to several days to take effect.[13,14,16,20,23,26] Additionally, in some patients the psychosis responds to the administration of chlorpromazine hydrochloride,[7,9] phenobarbital,[17] haloperidol given intramuscularly[22] or pentobarbital given orally.[20] In others, administration of phenytoin (Dilantin)[7] or barbiturates[12] is required for control of seizures. Recently propranolol, 60 to 160 mg per day, given orally in three to four divided doses, has been shown to be effective in controlling all of the symptoms of diazepam withdrawal.[27,29]

Because diazepam is such a widely prescribed drug, physicians should be aware of the potential of withdrawal reactions associated with this agent. The condition can be prevented by ensuring that use of the drug is not abruptly discontinued. Unexplained anxiety, agitation, confusion, disorientation or frank hallucination, as well as tremors or myoclonic jerks, occurring together or independently, should alert clinicians to consider diazepam drug withdrawal. If diazepam withdrawal is implicated, intravenous or intramuscular administration of 5 mg of diazepam may abort the acute reaction. Then diazepam or propranolol should be administered orally until symptoms completely resolve. The use of both drugs is discontinued by progressively decreasing the dosages.

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Acute Idiosyncratic Reaction to Hydrochlorothiazide Ingestion

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ADMINISTRATION OF THIAZIDE DIURETICS has been reported to produce various idiosyncratic reactions including skin rash,[1] urticaria, photosensitivity,[2] jaundice, necrotizing vasculitis[3] and bone marrow depression.[4-7]

There have been six reported cases of idiosyncratic pulmonary edema reactions immediately following the ingestion of hydrochlorothiazide.[8-12] These previously reported cases have not been associated with bone marrow depression. We report a case of hydrochlorothiazide-induced acute pulmonary edema and associated severe leukopenia and thrombocytopenia in a patient shortly after she ingested a single 50-mg tablet of hydrochlorothiazide.

Report of a Case

A 50-year-old woman entered the Los Angeles County-University of Southern California Medical Center emergency room in April 1980 because of nausea, vomiting and light-headedness. She had been in her usual state of good health aside from a history of mild hypertension, untreated except for salt restriction. The day of admission she had seen a physician and was given hydrochlorothiazide for mild hypertension. Two and a half hours after taking the first 50-mg tablet, nausea and vomiting developed and she became light-headed. She took no other medication.

She stated that a similar problem had occurred two years previously after taking hydrochlorothiazide and she had not taken the drug again. She said she had had no previous cardiac or pulmonary disease. She did not smoke.

On physical examination she was noted to be slightly obese and appeared mildly distressed. Her skin was diaphoretic and cool. Blood pressure was 90/60 mm of mercury without postural changes, pulse rate was 110 beats per minute and regular, respirations were 18 per minute and the temperature (taken orally) was 35.8°C. There was no neck vein distension. Auscultation of the chest showed decreased breath sounds at both lung bases. On examination of the heart she had neither murmurs nor gallops. There was no calf tenderness, clubbing or edema. The remainder of the examination showed no abnormalities.

Admission laboratory data within normal limits included serum enzymes, bilirubin, calcium, phosphorous, blood urea nitrogen, creatinine, serum albumin, total protein and serum electrolytes. Analysis of urine gave normal findings. The initial leukocyte count was 1,200 per cu mm, with 40 percent segmented neutrophils, 58 percent lymphocytes and 2 percent monocytes. No eosinophils or band forms were seen. The antinuclear antibody titer was positive at 1:20. The hemoglobin level was 15.4 grams per dl, hematocrit 45.2 percent and the platelet level appeared to be decreased. The electrocardiogram appeared unremarkable, but the chest x-ray study showed pulmonary edema (Figure 1) when compared with a normal film taken two months earlier (Figure 2).

The arterial blood gas determinations made 24 hours after admission while the patient was breathing room air showed an oxygen partial pressure of 74 mm of mercury, a carbon dioxide partial pressure of 30 mm of mercury and a pH of 7.47. The platelet count was 86,000 per cu mm. Various viral titers were negative, including cold agglutinins and complement fixation for histoplasmosis and coccidioidomycosis.

On admission to hospital, initial treatment included administration of oxygen and intravenous replacement of fluids. The patient responded well and had no further respiratory distress; no systemic corticosteroids or other medicines were given. The leukocyte count rose to 6,700 per cu mm after four days, with a normal differential count, and the platelet count returned to within normal limits. She was discharged after four days in hospital; no abnormalities were noted on an x-ray film of the chest.

Discussion

In view of the present widespread use of thiazide diuretics, the life-threatening adverse effects of these compounds are of great practical import. The spectrum of other significant drug-induced pulmonary disease has been reviewed in the past.[13] The previous reports of thiazide-induced pulmonary edema were not associated with severe bone marrow depression, though bone marrow depression due to the ingestion of hydrochlorothiazide has been reported,[4-7] and at least one case of hydrochlorothiazide-induced pulmonary edema was associated with moderate leukopenia.[12] Thiazide diuretics are frequently prescribed for edematous states and often for congestive heart failure. In our patient there had been no previous history of organic heart or pulmonary disease; as a matter of fact, the patient had had normal findings, except for transient hypertension, at a clinical examination two months earlier.

Apparently a similar reaction had occurred earlier in this patient after ingestion of a single thiazide tablet. The sequence of events following the last oral ingestion of a single thiazide tablet suggests an idiosyncratic re-

Refer to: Prupas HM, Brown D: Acute idiosyncratic reaction to hydrochlorothiazide ingestion. West J Med 1983 Jan; 138:101-102.

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action to thiazide, though the earlier history suggests prior sensitization is possible. If the pathogenesis had been on the basis of an allergic reaction, the patient may have benefited from corticosteroid therapy, but this was not instituted.

Although in this case and previous reports hydrochlorothiazide definitely appears to be causal, in only one instance was the patient again given the drug and the causal effect verified.[10] It seems unwarranted in our case to risk a second untoward reaction to prove the association was causal. The temporal relationship of the idiosyncratic reaction and the oral ingestion of a single tablet incriminates the diuretic.

From other published reports it is clear that a small number of patients have been recognized to have severe untoward reactions to taking thiazide diuretics, and presumably there are some patients who have a similar sequence of events but who go unrecognized. Even so, this is a most unusual response to such a commonly prescribed drug. It should alert physicians to serious reactions from the ingestion of a commonly prescribed drug.

Figure 1.—Chest x-ray film taken on admission showing bilateral interstitial pulmonary edema with a normal heart size.

Figure 2.—Chest x-ray film taken two months before admission showing clear lung fields and a normal heart size.

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Mycobacterium xenopi Pulmonary Disease

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Mycobacterium xenopi is a nontuberculous mycobacterium that has been classified as a Runyon group III organism in the past along with the related *Mycobacterium avium-intracellulare* complex, with which it is sometimes confused.[1] It is a scotochromogenic organism that can cause in humans clinical infection resembling pulmonary tuberculosis. Recognized infection with this organism is uncommon, with only five reported cases in the United States.[2-5] Unlike organisms isolated from

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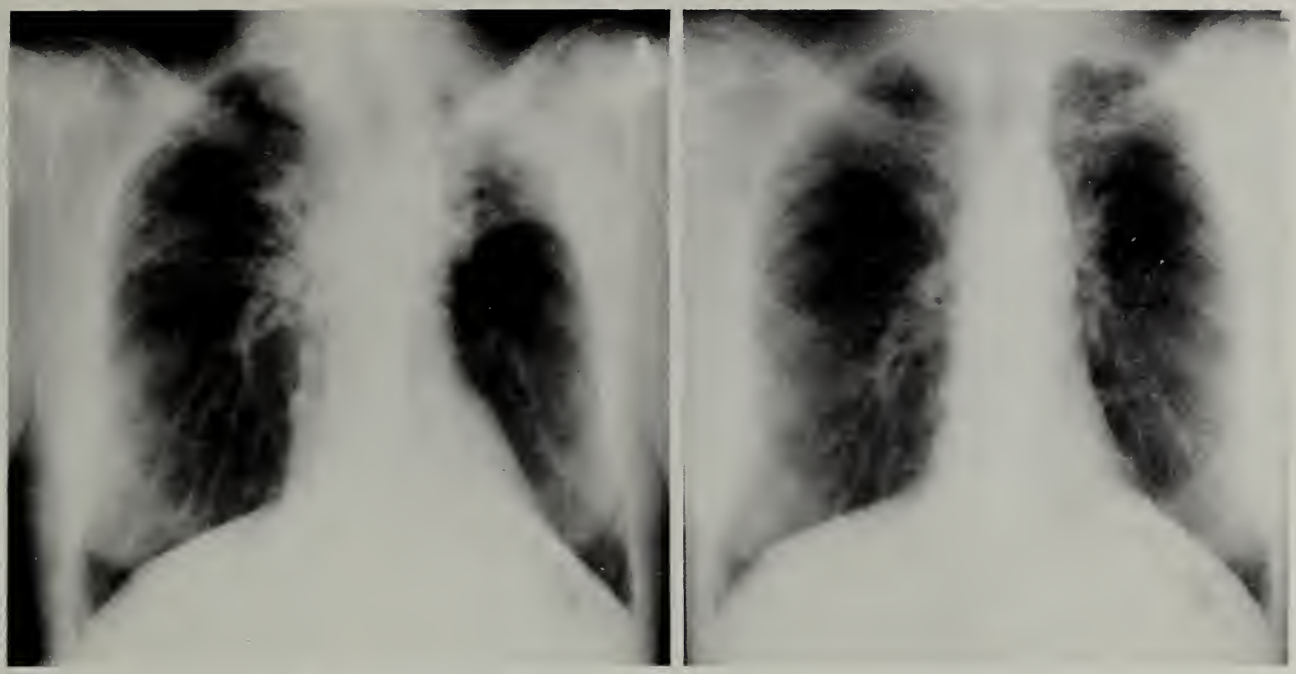

Figure 1.—Chest films. **Left,** Admission chest film. Bilateral upper lobe infiltrates. **Right,** Chest film 12 months after initiation of antituberculosis therapy.

infections with the related *M avium-intracellulare* complex, which are often resistant to antituberculosis drugs, organisms of *M xenopi* are sensitive to most drugs. Herein we describe the case of a man with chronic obstructive pulmonary disease and chronic bronchitis in whom a pulmonary infection with *M xenopi* developed and who showed a good response to antituberculosis chemotherapy.

Report of a Case

A 65-year-old retired railway conductor was admitted to Palo Alto (California) Veterans Administration Hospital because of a history of several months of malaise, anorexia, weight loss and chronic cough productive of yellow sputum and of the recent onset of chills, fever and night sweats. Past history was notable for severe chronic obstructive pulmonary disease and a 90 packs per year history of cigarette smoking. His medications included aminophylline and terbutaline. He stated he had no exposure to tuberculosis and several past tuberculin skin tests had been negative. He served in the US Army in Europe in World War II, but had not been out of the country since then. Over the preceding several months, he was treated with several alternate courses of tetracycline and ampicillin for presumed exacerbations of his chronic bronchitis. There was no improvement in his symptoms and he was admitted to hospital for further evaluation.

On physical examination he appeared wasted and chronically ill. His temperature was 38.5°C (101°F). Chest examination findings were notable for hyperresonance with a prolonged expiratory phase and occasional scattered expiratory wheezes. There was no significant lymphadenopathy. A roentgenogram of the chest showed bilateral apical infiltrates, which were not present on films taken four years before admission (Figure 1, left). Skin testing resulted in 7 mm of induration with 5 tuberculin units of standard tuberculin purified protein derivative (PPD-S) and negative reactions with PPD-Y *(Mycobacterium kansasii)* and PPD-B (Battey bacilli). Serologic studies with histoplasmin, coccidioidin and blastomycin were negative. Cultures of a sputum specimen were negative for fungi and cytologic studies showed no malignant cells. Ziehl-Neelsen stains of the sputum were positive for numerous acid-fast bacilli. After six weeks, three sputum cultures each contained more than 100 colonies of acid-fast bacilli. On initial isolation, the colonies were not pigmented and were felt to be *M intracellulare*. On subculture, however, they became increasingly yellow and biochemical testing confirmed their identification as *M xenopi*. Sensitivity testing showed sensitivity to isoniazid (INH), rifampin, streptomycin, kanamycin, ethionamide, cycloserine, and para-aminosalicyclic acid and resistance to ethambutol.

As a result of the identification of acid-fast bacilli on the smears he was treated initially with administration of 600 mg of INH and ethambutol hydrochloride, 15 mg per kg of body weight, daily with gradual clinical improvement. Following the isolation of *M xenopi* and the results of sensitivity testing, therapy was changed to INH, 600 mg; rifampin, 600 mg, and streptomycin 1 gram administered daily. On this regimen there was continued clinical improvement during the next few months and repeated sputum cultures were negative for mycobacteria.

After six months of treatment, severe liver function abnormalities appeared and were associated with fever, chills and peripheral eosinophilia. A diagnosis of INH hepatitis was considered likely. After INH therapy was discontinued, his liver function tests showed return to normal values, and he felt well. He has remained clini-

TABLE 1.—*Clinical Features of Patients With Pulmonary Infection With* Mycobacterium xenopi

	Age, Sex	*Clinical Features*	*Findings on Chest X-ray Study*	*Associated Disease*	*Treatment*	*Outcome*
This case report	65, ♂	Cough, sputum, fever, chills, night sweats, weight loss	Bilateral upper lobe infiltrates	Chronic bronchitis	INH therapy discontinued after 6 months; rifampin; streptomycin	Survived
Doyle et al, 1968[2]	72, ♂	Cough, sputum dyspnea	Bilateral upper lobe infiltrates	None mentioned	Refused	Died after 10 weeks
Fields et al, 1969[3]	53, ♂	Cough, chest pain, weight loss	Right upper lobe cavitary infiltrate	Concurrent *Histoplasma* infection	INH, PAS and streptomycin given	Survived
Elston and Duffy, 1973[4]	52, ♂	Cough, sputum, weakness, weight loss	Right upper lobe cavitary infiltrate	Bullous emphysema, alcoholism, gastrectomy	INH, ethambutol, streptomycin. Rifampin and PAS added later	Improved, but died suddenly 16 months later
Tellis et al, 1977[5]	50, ♂	Asymptomatic	Right upper lobe infiltrate	Chronic bronchitis	INH and ethambutol given	Survived
Tellis et al, 1977[5]	42, ♀	Anorexia, night sweats, weight loss	Left upper lobe infiltrate	Right upper lobe lobectomy 4 years earlier for adenocarcinoma	INH and ethambutol given	Survived

cally well since then on a regimen of rifampin, 600 mg given daily, and streptomycin, 1 gram given intramuscularly twice a week. A chest x-ray film after 12 months of treatment (Figure 1, right) shows significant improvement when compared with his admission film. He has now received 19 months of therapy with a total course of 24 months planned.

Discussion

Although the microorganism *M xenopi* was first isolated in 1957 from a skin lesion in a South African toad, *Xenopus laevis* (and hence the name),[6] it was not recognized as a pulmonary pathogen in humans until the report of Marks and Schwabacher in 1965.[7] Often it has been difficult to determine which strains of atypical mycobacteria cause human disease, and which are simply colonizing the upper respiratory tract. In our case, the substantial growth of *M xenopi,* the absence of other explanations for the apical infiltrates and the clinical and radiographic response to chemotherapy all provided evidence that this microorganism was presumably the causal agent for this patient's pulmonary disease.

Interestingly, the patient's sputum culture was reported initially to contain *M intracellulare*. Subsequently this organism was identified correctly as *M xenopi*. Elston and Duffy[4] had pointed out that strains of the *M avium-intracellulare* complex can be confused with *M xenopi*—both formerly Runyon group III organisms—because of a number of common characteristics: similar growth rates, weak to moderate catalase activity, negative Tween hydrolysis and similar results of iron uptake tests. Additionally, as stressed by Tellis and co-workers,[5] the differentiation of *M xenopi* from *M avium-intracellulare* complex is important because, unlike other Runyon group III organisms, *M xenopi* is usually susceptible to most antituberculosis agents. Features that are useful in the identification of *M xenopi* are its gradual development of pigment, microscopic colonial morphology, thermophilia and a positive arylsulfatase test.

The habitat of *M xenopi* has been studied by several investigators.[1,8-10] It has been speculated that *M xenopi* might be associated with reptiles or sea birds because it has been found in the droppings of sea birds and sparrows,[1] and more commonly in the coastal regions than in the inland areas of the United Kingdom. Pigeon droppings have not been found to be a reservoir of this organism. Our patient stated he had not been exposed to birds or animals of any sort. Researchers have also recovered this organism from both hot and cold water taps,[8] and from the hot water generators of a hospital.[9] In one study of microbial organisms found in tonsils, 60 percent of the mycobacterial species were identified as *M xenopi*.[10]

The presentation and clinical course of our patient's pulmonary infection was similar to that of typical pulmonary tuberculosis, with the insidious onset of cough and sputum; with chills, night sweats, fevers and weight loss, and with apical pulmonary disease. In the other five American cases, the patients with pulmonary infection with *M xenopi* (Table 1) also presented in a similar fashion and, except for one asymptomatic patient, each had disease in the upper lobes. The only associated and perhaps predisposing condition in our patient was chronic obstructive pulmonary disease with chronic bronchitis. Chronic obstructive pulmonary disease was present also in two of the five previously reported cases; one other, the only woman, had had a lobectomy for adenocarcinoma of the lung.

Our patient was treated initially with administration of INH and ethambutol; rifampin and streptomycin were added later and ethambutol therapy was discontinued when the results of sensitivity testing became

available. Six months later, clinical improvement continued even though INH therapy was discontinued because of the development of severe abnormalities in liver function. A similar good response to two- or three-drug therapy was noted in the other patients with pulmonary infections with *M xenopi*. With respect to drug sensitivities, the organism isolated from our patient's sputum was sensitive to each of the antituberculosis drugs tested, except for relative resistance to ethambutol. The organism identified by Elston and Duffy,[4] on the other hand, showed relative resistance to INH. Because variable resistance to the primary antituberculosis drugs can occur, it remains important to do sensitivity studies with each organism in order to adjust chemotherapy to include at least two or three agents to which the organism is sensitive.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgement before publication.

Beeper Use on a Medical Service

TO THE EDITOR: Pocket paging systems (beepers) were introduced to the medical community more than 20 years ago. The advantages of beepers are obvious for physicians outside a hospital; however, there are problems with the use of beepers inside hospitals today. A beeper signals not only its bearer but also everyone within hearing distance,[1] frequently interferes with teaching conferences and may disrupt critical doctor-patient interactions. Because of these problems, we have studied patterns of beeper use by a group of housestaff physicians.

Thirteen interns (postgraduate year 1) on the medical services at the University of Colorado University Hospital (UCUH) and the Denver Veterans Administration Medical Center (DVAMC) were asked to make a record in a notebook of all beeper calls they received over six days. Three interns at UCUH were responsible only for intensive care unit (ICU) patients and admitted patients every third day. These three interns shared one beeper and carried the beeper only when admitting. Three interns at UCUH were responsible for ward patients only and seven interns at DVAMC were responsible for ward patients and some ICU patients. These non-ICU interns admitted patients every third day but each carried a beeper every day.

A notation for each beeper call was made in a 3- by 5-inch notebook, giving the time of the call, the present activity of the intern and the importance of the call. The importance was rated on a scale of 0 to 2 as follows: 0 indicated "relayed no relevant patient-related information"; 1 meant "relayed patient information that had no effect on present patient management"; 2 indicated "relayed important patient information that required immediate changes in patient management."

The 13 interns recorded 564 beeper calls on 26 admitting and 30 nonadmitting days. Interns received nearly twice as many calls on an admitting day (13.6) as on a nonadmitting day (7.0). Call classification profiles for each service are shown in Table 1. Overall only 14 of 565 calls (2.5 percent) were class 2, resulting in immediate changes in medical management. The interns responsible for the intensive care unit only received a higher percentage of class 2 calls (7.5 percent) than other groups. Only a single class 2 call occurred during the 30 nonadmitting days that were included in the study. Additionally, UCUH ward interns, with no intensive care unit responsibilities, received only 1 class 2 call out of 181 calls received.

TABLE 1.—*Beeper Calls by Service and Call Classification*

Location	*Call Classification** 0	1	2	*Unclassified*	*Total*
Intensive Care Unit (UCUH)	17 (25.3)	45 (67.2)	5 (7.5)	0	67
Wards (UCUH & DVAMC)					
Admitting	165 (57.5)	114 (39.7)	8 (2.8)	0	287
Non-admitting	152 (72.0)	50 (23.7)	1 (0.5)	8 (3.8)	211
TOTAL	334 (59.1)	209 (37.0)	14 (2.5)	8 (1.4)	565

DVAMC = Denver Veterans Administration Medical Center
UCUH = University of Colorado University Hospital

*Call classification according to text.

Overall, nearly 60 percent of all calls received were class 0, thus not relevant to patient care. However, the ICU interns received a much smaller percentage of class 0 calls (25 percent). Interns not primarily responsible for the intensive care unit received category 1 and 2 calls more frequently on admitting (43 percent) than nonadmitting (24 percent) days. Finally, 37 percent of all calls occurred during a significant patient-physician interaction or scheduled teaching activity of the Medical Service. Most of those calls also did not affect patient management.

This study has shown that (1) the majority of beeper calls do not affect immediate patient management; (2) interns responsible for new admissions and intensive care unit patients receive patient-relevant calls more often than other interns; (3) nonadmitting and non-ICU interns almost never receive beeper calls affecting immediate patient management, and (4) a significant proportion (37 percent) of beeper calls interrupt a teaching exercise or patient-physician interaction.

There is no doubt that beepers have facilitated contact with hospital personnel; however, every beeper call which interrupts the beeper carrier is also likely to interrupt other people.[2] There also is no evidence to show that beeper utilization by in-hospital physicians has improved patient care. Our data would suggest that an important fraction of beeper use is disruptive. More effective use of beepers by selected interns could mini-

mize the problems associated with beeper use without interfering with patient care.

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Head Injury and Video Games

TO THE EDITOR: The incidence of accident victims surviving severe head trauma is increasing due to recent advances in acute medical care. These patients commonly present with numerous medical complications requiring multiple medical procedures. The use of medications for seizure prophylaxis has become routine because of the possibility of seizure disorders.

The recreational use of video games is rapidly increasing. In addition, video games present an attractive potential for remedying the cognitive impairments that often limit the adjustment of closed head injury survivors.

Last year we saw a 32-year-old man injured in a motorcycle accident. He sustained severe closed head injuries and a T-6 fracture-dislocation and resultant incomplete paraplegia. During the acute phase, he had several complications including hydrocephalus, which required placement of a ventriculoperitoneal shunt. In addition, during three months of acute care, he was placed on a regimen of phenobarbital, 30 mg given four times a day, as a prophylactic measure against seizures, although no clinical seizures were noted.

The patient's progress in the rehabilitation unit appeared to be hampered by his diminished level of alertness. No clinical seizures were observed, and an electroencephalogram showed no epileptiform discharges, although no visually evoked electroencephalograms were obtained. Consequently the administration of phenobarbital was discontinued in an attempt to improve his participation in rehabilitation. This resulted in an apparent increased level of participation with the patient able to return home following three months of intensive rehabilitation.

Approximately a week following discharge, after playing a popular video game for two hours without interruption, he had a grand mal seizure and phenytoin (Dilantin) was given intravenously. Therapy with phenytoin continues and the patient has had no other seizures. Visually evoked electroencephalograms are pending.

The patient's history suggests that certain head-injured patients may be vunerable to visually evoked seizures following prolonged use of video games. Caution in the recreational or therapeutic use of video games with this patient population may be indicated. Further inquiry is required.

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Why Three?

TO THE EDITOR: In a simple parlor game participants are asked to select a number from one to ten and write it on a piece of paper. About 50 percent of people select the number three. Why? Speculation is that it is a "safe" number, not the smallest and not the largest, and that it alone has perfect symmetry, a beginning, a middle and an end. Or perhaps there is something built into our culture and our consciousness that makes three a lucky and a special number.

The Kaballah, an ancient Hebrew religious book that is obsessed with numerology, cites many important groups of three—for example, three elements: water, air and fire; three important body parts: heart, stomach and head; three great attributes: "crown," wisdom and intelligence; three characteristics of man: substance, thought and life. In the Kaballah, except for the number one (one deity), no number is more important than three, and perhaps seven. And in Christianity there is of course the power and importance of the Holy Trinity.

Medicine, too, has its "holy trinities." In hospital orders the number three occurs with great frequency and sometimes with little rationale. Blood cultures are often ordered times three. Why three? Washington[1] in his chapter on the diagnosis of endocarditis in the *Todd-Sanford-Davidsohn* laboratory manual, states that "two sets of blood cultures are sufficient." The text also states that for the diagnosis of other bacteremias "collection of more than three sets of cultures [in 24 hours] should be performed only following consultation with the laboratory director." Tests of stool specimens for occult blood are commonly ordered times three. Moreover, the test kits used for outpatients are designed to be done on three successive days.

In a patient suspected of having myocardial infarction, electrocardiogram (ECG) and enzyme studies are often routinely ordered times three. Why? The creatine kinase MB band will be positive within the first day and is more specific than the serum aspartate aminotransferase (formerly SGOT) and the lactic dehydrogenase. While the ECG findings may not be abnormal in the first few hours after an infarction, they certainly will be by the second day. If it is necessary to observe the evolutionary changes, then more than three days are needed. Many hospitals require intermittent positive-pressure breathing orders and orders for antibiotic administration to be renewed every 72 hours—three days. Why three? Sputum cultures for tubercle bacilli are ordered three times. On what basis? I often hear my colleagues say that patients cluster in threes, that is, death often comes in threes, cancer-diagnosed patients come in threes, and so forth. Three is also a favorite

prognostic number, that is, "Take this medicine for three days and call back"; or, "Wait three days and then we'll consider a different approach."

The medical fascination with three may be built out of solid clinical experience or scientific reason. But like all traditions and "routines" it deserves reexamination to be certain that we are being cost effective and efficient. It may turn out that there is a certain amount of magic in our medical three that is as mystical as the Kaballah.

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Interaction Between Valproic Acid and Phenytoin

To the Editor: I enjoyed reading the succinct and educational "Epitomes of Progress, Neurology—Important Advances in Clinical Medicine" in the October issue. Nevertheless, in her effort to be brief, Dr Doris Trauner[1] may have left room for a potentially hazardous interpretation. She states, "Valproic acid . . . decreases phenytoin concentrations, so that blood concentrations of [this medication] should be monitored closely when used in combination with [valproic acid]." From this it would not be unreasonable for the reader to make a common assumption that if the serum concentration of the interacted drug falls below the usual "therapeutic" range, the dose should be increased. It is true that the effect of the common interaction, wherein the metabolism of drug A is stimulated by drug B, can be overcome by increasing the dose of A. This remedy *cannot* be used for the phenytoin/valproic acid interaction. While total serum phenytoin may decrease with the addition of valproic acid, the fraction of remaining phenytoin not bound to plasma protein increases. The actual concentration of this free phenytoin may unpredictably decrease,[2] remain constant[3] or increase[4] from prevalproic acid levels. The paradox of this interaction has been well documented[5] and there are recommendations that phenytoin dosage not be altered on the basis of this anticipated interaction alone.[3,6] Unfortunately, monitoring total serum phenytoin concentrations as a measure of therapeutic success or impending toxicity will prove unreliable, not helpful and even misleading.

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Covert Diuretic Use and Anorexia Nervosa

To the Editor: In the October 1982 issue there appeared an article by Drs Spratt and Pont entitled "The Clinical Features of Covert Diuretic Use."[1] In this article the authors described the cases of two patients with covert diuretic abuse. Both of these patients, on the basis of the information provided in the article, should carry the psychiatric diagnosis anorexia nervosa. Most psychiatrists would immediately suspect that a person who took diuretics or laxatives (or both) covertly has an eating disorder. Indeed some of the other information provided in the article pointed strongly in that direction.

The baffling thing about the presentation to me is that these patients could be treated for "covert diuretic use" without addressing the real problem. Although it was a fine article and I am sure Bartter's syndrome is an entity I should know about, I am more sure that anorexia nervosa is something that the authors should know about.

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Non-Hodgkin's Lymphoma in Homosexual Men

To the Editor: As has been recently reported, the male homosexual population is at increased risk for certain tumors.[1] Recently, Ziegler and co-workers[2] observed another malignancy that may have an increased incidence in homosexual men. They reported four cases of a Burkitt's-like lymphoma in male homosexuals, thus adding another malignancy that may be associated with a male homosexual life-style. In the past year we have also observed two such cases of lymphoma in homosexual men:

Patient 1. A 29-year-old homosexual man was evaluated for increasing abdominal girth in January 1980. On physical examination an abdominal mass was found. At laparotomy, a biopsy specimen showed a Burkitt's-like lymphoma. The patient was treated with combination chemotherapy (cyclophosphamide-doxorubicin-vincristine-prednisone, or CHOP). Following an initial response complicated by the tumor lysis syndrome, the patient had progressive disease resistant to further therapy and died in March 1980.

Patient 2. A 27-year-old homosexual man was admitted to hospital for evaluation of an abdominal mass.

At laparotomy, a biopsy specimen of an omental node showed a Burkitt's-like lymphoma. The patient was treated with combination chemotherapy (CHOP) and remains in a remission.

Of interest, both of our patients engaged in homosexual relations with numerous partners over many years. In addition, each experimented with various street drugs. Cytomegalovirus and Epstein-Barr virus titers were elevated in both of our patients, though no further studies were carried out.

Based on the report of Ziegler and associates, as well as the additional cases observed by us, it appears that a Burkitt's-like lymphoma may occur in homosexual men. Further investigations are needed to define risk factors and develop suitable screening methods.

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California Legislation Regarding Patients With Breast Cancer

To the Editor: On October 9, 1982, a symposium titled "The Current Management of Early Breast Cancer," sponsored by Western Medical Center, St. Joseph's Hospital, and the Clinical Oncology Service of the University of California, Irvine, California College of Medicine, was held in Anaheim, California. It was evident that the best available data on treatment of breast cancer are retrospective and could be used to support widely divergent views of the basic biology and appropriate clinical approach to the disease. At the same conference a new California law requiring that physicians discuss a list of specific diagnostic and treatment options with their patients with breast cancer was discussed. However, physicians have not been provided with materials or directives for their presentation to a patient. The Honorable David Roberti, state senator and author of the law, described its origin: a woman disagreed with her physician that she needed a mastectomy, signed out of the hospital, read extensively about the disease, decided to receive radioactive implants and has subsequently done well after an unspecified period of time.

The long-range implications of legislation influencing medical practice were alluded to at the symposium. Not discussed, however, were its potential adverse effects on physician-patient communication and rapport. True, the law will protect inquisitive patients from poorly informed or inflexible physicians. However, some patients react to the news of breast cancer with shock, fear and disbelief. Overly anxious patients, hoping that their physicians will resolve uncertainties and provide firm guidance, may be immobilized by the presentation of conflicting alternatives at a time when their ability or willingness to assimilate it is limited.

Several guiding principles may help physicians in this situation. First, physicians should reassure their patients with newly diagnosed breast cancer that disagreement about treatment does not imply lack of hope and that referral to multiple specialists does not imply loss or dilution of the primary doctor-patient relationship. Second, patients who do not spontaneously request information or discuss alternatives should be encouraged in a nondirective manner to share their experiences, beliefs and fears about cancer and its treatment. In this way patients may be helped to formulate the questions that the law requests we answer, and by asking them they will indicate the proper time to present the materials. Finally, patients who become anxious when you provide the materials should be reassured that you will take as active a role as necessary in helping them decide how to proceed.

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Pulmonary Effects of Intestinal Parasites

To the Editor: During a recent one-month tour of duty at the Lyndon B. Johnson Tropical Medical Center in American Samoa, another visitor, a radiologist, showed me x-ray films of 15 children with chronic chest infiltrates. These occurred primarily in the right middle lobe and perihilar regions. In some of the children repeated x-ray studies had been done over two years showing some shifting patterns, but no resolution of pneumonia. Three had significant eosinophilia noted in their charts. In all of the children chronic coughing or wheezing had been noted. Antibiotics had had no effect.

My immediate conclusion was that most of these children were suffering from the larval migrans effects of intestinal parasites. The larvae of intestinal helminths develop in the lungs where they cause direct irritant and obstructive effects, while the worms themselves may be highly allergenic.[1] In fact, on examination of a single stool specimen for each child, seven contained eggs of either *Ascaris* or hookworms. Later specimens from the other children may show positive results on testing as larvae mature and move to the intestines. Another possible cause, pulmonary effects of filaria,[2] was not investigated during my stay. Approximately a third of the children in the outpatient department presenting with wheezing or coughing that had lasted longer than two weeks were also found to have helminth eggs in a single stool specimen during the one-month period.

These cases reminded me of an old teaching, "All that wheezes is not intrinsic asthma." In the West, where we see many patients from the Far East, Pacific and Central American regions where helminths are highly endemic, it would be well for us to remember to check for the presence of these parasites in new immigrants who wheeze, cough chronically or have

persistent pneumonia. The parasites are also found in the United States, especially the southeast.[3] It would not be unreasonable to examine a stool specimen of any difficult to manage asthmatic patient, especially if there is any indication of chronic changes on x-ray studies.

Unfortunately, since larvae may be present in the lungs with no worms in the intestine, both diagnosis and treatment may require close follow-up checks. Mebendazole (Vermox), which is the best initial drug for helminths,[3,4] is poorly absorbed systemically.[5] Hence, one must treat the patient symptomatically and then in approximately two months, when larvae have left the lungs, retreatment with mebendazole should eliminate the worms unless reinfection occurs. Then the patient should be symptom free and use of other medicines such as bronchodilators can be withdrawn.

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Hospice Care

To the Editor: "Commentary From Coeur d'Alene: Care for Terminally Ill Patients" by E. R. W. Fox, MD,[1] reflects the growing awareness among physicians of the benefits of hospice care and the entire hospice movement.[2] The unique concerns of the hospice movement are the management of terminally ill patients in such a way that they live until they die, that the family lives with them as they are dying and that the family members go on living after their loved one dies. The most significant feature and concerns of hospice care include not only expert symptom management and pain control, but attention to psychological, sociological, spiritual and financial concerns. No professional group possesses all of the knowledge required to deliver hospice care; these comprehensive care measures can only be delivered by a truly multidisciplinary team.

The National Hospice Organization (NHO), with cooperation from national health care organizations and leaders in the field of hospice care, has been working diligently to answer the questions related to quality of care, facilities and personnel that Dr Fox mentions in the latter part of his commentary. The standard documents that currently guide hospice care can be obtained by writing to the NHO.

Dr Fox states that "the medical profession has joined in giving tacit support to the hospice movement." We need to give more than tacit support. We must take a very active role and provide leadership for the hospice movement in this country. In 1980 the Association of Hospice Physicians (1211 A. Dolly Madison Boulevard, McLean, VA 22101) was formed. I strongly encourage all physicians who want to learn more about the hospice movement and its principles of hospice care to join that organization.

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Preoperative Medical Evaluation

To the Editor: I enjoyed the article by Drs Elliot, Linz and Kane in the October issue.[1] It was succinct, brief and uncomplicated by excessively technical considerations.

One sentence caught my eye: "In this paper, we review the recent literature and provide an approach to perioperative medical management based on our experience with a general medicine consultation service at a university hospital." Does the sentence imply that patients going to surgery routinely receive a general medicine consultation? It behooves all physicians to sharpen their skills with regard to proper history-taking and performance of physical examinations, especially before any high-risk procedure, be it an operation, endoscopy or other relatively invasive procedure. All physicians, including ophthalmologists, orthopedists and psychiatrists, should have at least the basic knowledge contained in the article published by Drs Elliot, Linz and Kane and be able to apply it. Is it really necessary to "farm out" preoperative evaluation to another physician when the considerations outlined in the article should be clear to all MD's?

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Topics in Primary Care Medicine

Herpes Simplex Infections

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"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice that generally do not fall into well-defined subspecialty areas and are rarely discussed thoroughly in medical school, house staff training, textbooks and journals. Often the pathophysiology is poorly understood and clinical trials to assess the effectiveness of diagnostic tests or therapies may be lacking. Nevertheless, these problems confront practitioners with practical management questions.

The articles in this series discuss new tests and therapies and suggest reasonable approaches even when definitive studies are not available. Each article has several general references for suggested further reading. We hope this series is of interest and we welcome comments, criticisms and suggestions.

—BERNARD LO, MD
STEPHEN J. McPHEE, MD
Series' Editors

There has been a recent growth of interest in herpes simplex viruses prompted by a growing incidence of infection with these pathogens, and the availability of more effective therapies. In many medical practices herpes simplex is the most prevalent sexually transmitted disease. Herpes simplex also causes fever blisters, encephalitis, ophthalmitis and a virulent infection in neonates.

HSV Infections—General, Epidemiology, Incidence

The increased frequency of herpes infections is well documented. There has been a ninefold increase in the number of visits to office-based physicians for genital herpes infection from 1966 to 1979. Consultations for herpes labialis, herpes stomatitis and ocular herpes increased less than twofold during the same period.

HSV-1 is most commonly associated with infections of the mouth, lips, eyes, brain and skin above the waist. HSV-2 is usually responsible for urogenital infections, disease of the newborn and cutaneous lesions below the waist. Antibodies to HSV-1 which are present in up to 90 percent of an urban population occur with the greatest frequency between the ages of 1 and 4. There is a further slight increase in the prevalence of positive titers from 5 to 14. During adolescence the prevalence of antibodies to HSV-2 increases and continues to rise through young adulthood. Socioeconomic class is also a determinant of HSV-2 infection. In young adults belonging to lower socioeconomic classes positive antibody titers are found in as many as 85 percent. In a group of medical students studied for the presence of antibodies to HSV-2, only 40 percent were found to be positive.

HSV-1 is being found with increasing frequency in primary urogenital infections, perhaps due to an increase in orogenital sex. Genital infection with HSV-1 will continue to be less common than with HSV-2, however. Recurrent attacks in a person with HSV-1 genital infection are less frequent than with HSV-2 and preexistent HSV-1 antibodies provide some resistance to exogenous infection.

HSV-1 Infections—Initial, Recurrent

Gingivostomatitis is the most common symptomatic presentation of initial HSV-1 infection. It occurs most commonly in children 1 to 3 years of age. The anterior and posterior oropharynx may be covered with vesicles and shallow ulcers. Other commonly involved sites in-

Refer to: Glaser RB: Herpes simplex infections (Topics in Primary Care Medicine). West J Med 1983 Jan; 138:111-113.
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clude the tongue, gingiva and lymph nodes. Fever and general malaise frequently accompany the lesions. Finger suckers may develop an infection of the finger known as herpetic whitlow. Infectivity is high in exposed susceptible persons, and incubation is short—about three to five days. Viral cultures or the presence of multinucleated giant cells in cytologic specimens help confirm the diagnosis. Recurrences rarely take the form of stomatitis, but rather cause cutaneous eruptions of the lip (herpes labialis), nose or cheeks.

Primary HSV-1 infection may involve cutaneous sites anywhere on the body, although it is infrequent below the waist. Recurrent lesions will frequently appear in the same general vicinity as the initial eruption.

Initial infections involving the skin may also be accompanied by fever, malaise and lymphadenopathy. In persons with atopic eczema, Wiskott-Aldrich syndrome or other diffuse dermatoses, widely disseminated cutaneous lesions known as Kaposi's varicelliform eruption may develop. More localized skin involvement may be confused with pyoderma, contact dermatitis or herpes zoster.

Herpes labialis results from reactivation of latent infection that remains in regional sensory ganglia following stomatitis or clinically inapparent HSV-1 infection. A prodrome characterized by burning or hyperesthesia precedes the eruption by one or two days in about 60 percent of patients. Grouped vesicles on an erythematous base evolve over about 48 hours to form crusts, and resolve completely in from one to two weeks. The pain is maximal at 24 hours and then declines rapidly. Factors known to trigger recurrences of skin and lip lesions include ultraviolet light, menses, fever or emotional stress. Recurrences may be complicated by erythema multiforme. Attempts to intervene therapeutically with antiviral agents have been hampered by the fact that viral replication peaks at about 24 hours and then declines rapidly. To be effective any intervention would presumably have to be undertaken at the very first sign of recurrence. There is no treatment of proven efficacy, although acyclovir (Zovirax) may ameliorate the eruption if used early.

Ophthalmitis

Herpetic keratitis may be a manifestation of primary or recurrent infection. Lesions are usually unilateral, but both eyes may be involved in up to 6 percent of patients. Deeper involvement with hypopyon, uveitis or iridocyclitis may occur spontaneously or result from inappropriate treatment with topical steroids. On examination of herpes keratitis using fluorescein staining, characteristic dendritic (branched) ulcers are seen. Topical administration of idoxuridine or trifluridine is effective in the treatment of acute cases. About 30 percent of patients have a recurrence within two years.

Encephalitis

Herpes simplex encephalitis is a devastating manifestation of HSV-1 infection. Focal motor and sensory deficits, seizures, aphasia and temporal lobe involvement are typical features of the disease, but they are not sufficiently distinctive to allow confident differentiation from other causes of encephalitis. Noninvasive diagnostic techniques including electroencephalography and brain scanning may have distinctive features, but are not specific enough early in the disease when treatment must be instituted. Brain biopsy remains the gold standard for diagnosis. Of those patients who present with features consistent with herpes encephalitis, 25 percent will have diseases requiring therapy other than ara-A (vidarabine), the current standard for the treatment of herpes encephalitis. Vidarabine has been shown to decrease mortality by about 50 percent, but its long-term potential adverse effects remain unknown. It is for these reasons that empiric therapy of suspected herpes encephalitis without previous biopsy is not recommended.

HSV-2 Infections—Initial, Recurrent

Urogenital involvement, the most common manifestation of disease caused by HSV-2, is the focus of much of the current interest in herpes simplex virus infection. It is this aspect of herpes infections, with the attendant psychosocial ramifications and concern with cancer and possible transmission to neonates, that has generated so much concern.

In women, initial disease usually occurs within two to seven days following exposure and typically presents with wavelike crops of vesicles that coalesce to form bullae or large tender ulcers involving the external genitalia. The cervix and vagina are commonly involved in initial infections, but are infrequently affected during recurrences. Systemic symptoms including fever, headache, myalgia and abdominal pain accompany genital lesions in most women. Pain from the involved areas is frequently severe and does not begin to decline until about the tenth day. Inguinal and pelvic pain may also result from lymphadenopathy or radiculitis. Severe dysuria or neurologic dysfunction may lead to urinary retention. This syndrome is generally self-limited and regresses with only supportive treatment. Aseptic meningitis occurs in approximately 6 percent of men and 14 percent of women with initial herpes.

Recurrent episodes of genital herpes occur in approximately two thirds of all cases in the year following the initial attack. In a third of women there is only one lesion, and in three fourths there are three or fewer. One study followed the frequency of recurrences and found that 53 percent of patients reported one or more per month, 33 percent one every two to four months and 14 percent less often than every four months.

Recurrent lesions in women usually cause pain and shed virus particles for an average of six to eight days. The presence of pain thus correlates well with recoverable virus. A prodrome of itching, burning and hypersensitivity precedes the eruption in up to 50 percent of recurrences. Prodromal neuralgia involving the ipsilateral buttock, groin, thigh, calf and foot is also com-

TABLE 1.—*Cesarean Section Recommendations in Patients With Herpes Simplex Infection*

Cesarean Section Recommended
Primary genital herpes at term with membranes intact or ruptured less than 4-6 hours.
Recurrent genital herpes at term with membranes intact or ruptured less than 4-6 hours.
Positive cervicovaginal culture or cytology for herpes at term.
Cesarean Section Not Recommended
Primary or recurrent herpes, or positive culture with membranes ruptured more than 4-6 hours.
Nongenital herpes (isolation of newborn from mother recommended until maternal lesions resolve).
History of herpes with no evidence of clinical disease at term.

mon. Most recurrences cannot be related to a specific precipitant.

Recurrences in men are associated with fewer than four lesions in 70 percent of patients. The duration of pain and virus shedding is generally less than in women, lasting an average of three or four days.

There is no cure for genital herpes. Topical acyclovir has recently been approved and released for this indication in immunocompromised hosts. It also seems to abbreviate the duration of pain and virus shedding in newly infected patients and men with recurrent lesions. There is no evidence that it affects the frequency of recurrence. Other unproved, even potentially harmful, therapies that have been advocated include use of photo dye inactivation, topical ether, lysine or whole virus vaccine.

To minimize the chance of transmission to an uninfected partner, intercouse should be avoided while there are clinically apparent lesions or pain. Virus is occasionally shed even in the absence of symptomatic lesions. The use of contraceptive vaginal foams, which are highly viricidal, or condoms may protect against transmission of infection.

Neonatal Herpes

One of the most dreaded complications of urogenital herpes (both HSV-1 and HSV-2) is its transmission to the newborn infant through an infected birth canal. Neonatal herpes has about a 60 percent immediate mortality, although recent results of treatment with ara-A have been promising. An additional 20 percent survive with significant sequelae, commonly neurologic and ophthalmologic. Maternal infection is more often inapparent (70 percent) than symptomatic. Epidemiologically, women delivered of infected babies are more likely to be young and nulliparous. Past history of herpes simplex virus infection in the mother or recent infection with the virus in the sexual partner significantly increases the risk of neonatal infection. Transmission has also resulted from infected nursery personnel. Skin lesions are the most common presenting manifestation, and progression to more generalized disease occurs in 70 percent of infants whose presenting sign is skin vesicles.

The risk is greatest in women who have active herpes infection at term and have vaginal delivery or who have ruptured membranes for more than four hours. Cesarean section greatly decreases the risk of infection of the infant if done within four hours after the rupture of the membranes. Primary infection at term confers the greatest risk because the virus titers are highest and maternal and therefore fetal antibodies are lowest.

In a high-risk situation (history of genital herpes in patient or sexual partner), weekly cervicovaginal viral cultures are recommended beginning in the 36th week. Cesarean section is recommended if there is a positive culture or clinical evidence of lesions at term.

Table 1 summarizes these recommendations.

Association of HSV With Cancer

The association between herpes simplex infections and cancer remains controversial. Neoplasms occur more commonly in sites predisposed to herpes infections. Cancer of the lip frequently occurs at the same site as recurrent herpes labialis. Herpes simplex infection of the cervix involves the squamocolumnar junction, the location of most cervical neoplasms. HSV-2 antigens have been found in a high percentage of pathologic specimens from patients with carcinoma in situ of the vulva, and as many as 38 percent of cervical cancer specimens.

Other evidence implicating herpes simplex virus as an oncogenic agent is seroepidemiologic. Retrospective and prospective studies have shown that women with cervical neoplasms have higher frequencies of HSV-2 antibodies or cytologically proved HSV-2 infection. Similar risk factors, however, predispose to both herpes simplex infection and cervical cancer. These include multiple and frequent sexual partners and initial sexual experience at a young age. The association, therefore, may be coincidental rather than causal.

Summary

Herpes simplex virus infections are increasing in frequency, and may involve the skin, mouth, rectum, urogenital tract and central nervous system. Infection in a newborn infant is frequently fatal, and promises to become a more frequent problem as the overall incidence of urogenital herpes infections continues to increase.

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Medical Education

Assessing Continuing Medical Education Needs in New Mexico

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In 1981 a decision was made by the University of New Mexico School of Medicine to create a new Office of Community Professional Education whose primary function was to create continuing medical education programs tailored to its constituency. To accomplish this, a needs assessment survey was distributed to a stratified random sample of members of the New Mexico Medical Society practicing throughout the state to determine preferred learning styles, locations of programs and times of year, as well as other determinants for attending such programs. The survey was received by 647 physicians and 469 returned them—a response rate of 72.4 percent.

Conclusions reached as a result of the needs assessment will serve as a basis of policy formation for the delivery of continuing medical education at the University of New Mexico School of Medicine.

Continuing Medical Education (CME) as a requirement for relicensure has been mandatory in New Mexico since 1972. New Mexico was the first state to enact such a requirement. A formal Office of CME was established in 1976 by the University of New Mexico School of Medicine, the only medical school in the state. During the next five years the role of the office evolved into a more far-reaching one. In 1981 a decision was made by the medical school's administration to create a new Office of Community Professional Education (OCPE), which absorbed the Office of Continuing Medical Education. The primary function of the new office was to create CME programs that were tailored to its constituency: doctors practicing throughout the predominantly rural state of New Mexico.

The OCPE's premise was that if a CME program was to be successful, it must be responsive to physicians and the communities they serve. It has been found that the majority of typical continuing education programs offered by accredited institutions or organizations are based on the concept of institutionally oriented planning.[1] Institutionally oriented planning is often dictated by the interests of the organization rather than the needs of the learners. CME opportunities in New Mexico were plentiful; the challenge was to establish a new system for it with maximum learner participation. This follows the educational theory, developed by John Dewey in the early 1900s and expanded in the past several years by Malcolm Knowles, that advocates a change from a subject-centered approach (what Knowles refers to as "teacher-directed") to a learner-centered approach (Knowles' "self-directed" learning).[2]

In order then to develop a new system of learner-centered CME, a means of developing two-way communication between the School of Medicine and community physicians was needed. The first link in this communication was to assess what New Mexico physicians thought about CME and what they wanted in this regard from the School of Medicine. To accomplish this, it was necessary to design and implement a needs assessment survey, the first step toward a learner-centered approach.

Refer to: Kantrowitz MP, DiVasto PV, Starks AM, et al: Assessing continuing medical education needs in New Mexico (Medical Education). West J Med 1983 Jan; 138:114-117.

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Needs assessment surveys for CME were described by Tye and co-workers from the University of Iowa College of Medicine in 1978.[3] The Iowa study sampled every physician in the state to determine CME needs in emergency medicine. Results indicated a desire for more programs emphasizing basic clinical procedures.

Vaughan and associates from the University of Texas Health Science Center in 1979 investigated preferred CME formats and sponsoring agencies, surveying a random sample of physicians in the Texas Medical Association.[4] It was found that most respondents felt their present CME activities were satisfactory; however, location, cost, topic and amount of available time were factors in lack of participation. Texas physicians preferred specialty societies as a source for their CME.

A similar study was reported by Stinson and Mueller from the University of Alabama, Birmingham, in 1981,[5] using interviewing rather than a mailed questionnaire. Selected health professionals were questioned about their CME habits and sources of information. Results indicated that continuing education courses offered by a nearby medical school were the fourth most common choice for CME. Health professionals in "semiurban" areas indicated a desire for programs held locally and audiovisual materials.

Curry and Putnam[6] investigated learning styles of all practicing physicians in the Maritime Provinces of Canada in 1981 to compare the CME methods that physicians stated they preferred with the methods they actually used. For example, a fourth of the respondents stated that they preferred clinical traineeships and another fourth preferred traditional CME conferences; however, most indicated that reading was their actual source of continuing education.

While these studies offered some direction for a needs assessment survey, it was felt that the information learned was not sufficient for us to generalize to the likely needs of physicians practicing in New Mexico. The OCPE decided that in order to formulate worthwhile policy direction for the delivery of CME to New Mexico physicians, a comprehensive needs assessment must be carried out. This paper discusses the needs assessment that was done and the policy directions that were indicated after analysis of the results.

Methods

To develop a needs assessment questionnaire the OCPE assembled a task force that included a physician (Assistant Dean for OCPE), an outreach coordinator, a psychologist and a nurse practitioner—all of whom had wide-ranging experience working with physicians throughout the state. Meetings were held over a five-month period in which results from earlier surveys were studied, sample questions were suggested and various formats were discussed. From these data, questions were devised to discover what was considered worthwhile by practicing physicians, the School of Medicine's faculty and the OCPE. The flow of questions followed a time grouping: the first set investigated present demographic information, the second set asked about past and present CME experiences, the third set questioned learning styles and most appropriate setting and the fourth set collected marketing data and information concerning CME services and topics that could be offered by the School of Medicine. The instrument was designed for ease of answering, computer compatibility and brevity. While most questions were scaled (on a 1 to 6 Likert scale), several were open-ended.

After selection of questions and format, the instrument was field tested with 15 physicians who were representative of the group to be sampled. Questions were then revised and put into final form. A total of 27 questions were selected. At the time of the survey, there were approximately 1,600 physicians licensed to practice in New Mexico and residing in the state. This was determined from the New Mexico Medical Society roster, which accounts for more than 95 percent of physicians practicing in New Mexico. Because cost factors prevented a survey of the entire subject pool, the subjects chosen were a stratified random sample of physicians, representing all specialties practicing in New Mexico. The sample size was 700. For stratification purposes, the number of practitioners in each specialty was determined for each of the 33 counties in the state. If a specialty had fewer than four representatives in any county, all were surveyed. If there were more than 4 but fewer than 50, half were surveyed. If there were more than 50 subjects in any given specialty, a third were included. This stratification was done to obtain a larger sample of rural physicians than would have been possible by using a simple random method. This methodology allowed the OCPE to learn of the CME needs of rural physicians as well as those of their urban counterparts practicing in New Mexico.

In an attempt to assure a high response rate, a cover letter signed by the Assistant Dean for OCPE and the Chairs of each of the specific clinical departments accompanied every questionnaire, personally requesting participation in the survey.

After the initial mailing, each subject was given three weeks to respond. If he or she did not, OCPE staff phoned the physician's office to request a response. Following the phone calls, a second mailing was sent to those who indicated they had not received the questionnaire. As each questionnaire was returned, a code number was assigned and used throughout the analysis of the data to assure anonymity.

Results

The total number of questionnaires mailed and delivered was 647 (of the 700 questionnaires, 53 were returned as undeliverable). After the first three-week period, 377 were returned (80 percent of total questionnaires returned) and 92 questionnaires were returned after the second period (20 percent of total questionnaires returned). The final response rate was 72.4 percent (N = 469).

Of the 27 questions in the survey, 9 had specific policymaking implications (see Table 1). Responses were solicited from physicians in 15 specialty areas.

However, the responses of nine specialties make up 87 percent of the total responses, and will be the subject of discussion in this paper. These were emergency medicine, family practice, internal medicine, obstetrics/gynecology, orthopedics, pediatrics, psychiatry, radiology and surgery.

An open-ended question was asked in regard to how present CME could be improved. More than half of the subjects responded to this question. Interest was shown in having more local courses and more specialty-oriented courses, and a general need was expressed for a greater volume of courses. Also requested were problem-based courses with hands-on experience, video courses for home credit and mini-residencies.

When asked if the cost was an important factor in choosing CME programs, those physicians in specialty areas traditionally viewed as lowest-earning (general practice, internal medicine, pediatrics, nonsurgical specialties[7]) were most concerned with cost. However, traditionally high-earning specialty physicians (obstetrics/gynecology, general surgery, surgical specialties[7]) felt cost was not a factor (see Table 2).

When asked to rate ten approaches to learning CME, the majority of respondents rated the traditional slide and lecture format, seminars and workshops with hands-on experience as most helpful. Research paper presentations and teleconferencing were considered least helpful. Small conferences (fewer than 20 participants) were preferred over large conferences (more than 20 participants) by more than two to one (see Table 3).

In the next question, social and political functions of CME programs were rated by respondents. Relaxation, colleague interaction and availability of resort facilities were considered important factors by a majority of the total respondents. "Medical politics" rated lowest by a margin greater than five to one.

When physicians practicing outside of Albuquerque were asked if they would attend CME courses at the School of Medicine or some other Albuquerque location, 48 percent indicated it would be highly desirable to do so (N=277). When asked if they would prefer attending CME courses in their own town, 53 percent felt that would be highly desirable (N=266). Only 25 percent of the respondents who practice outside of Albuquerque indicated they would prefer attending CME programs at a regional center (N=244).

In response to a question on scheduling of CME, November was the most popular month for five of the specialties (internal medicine, obstetrics/gynecology, orthopedics, radiology and psychiatry). None of the physicians indicated an interest in December or Janu-

TABLE 1.—*The 9 Survey Questions (of a Total of 27) Having the Most Important Policymaking Implications*

1. How could your present CME be improved?
2. The most important reasons for choosing the CME programs you have attended in the last three years were:
   1. topic 2. time of the year 3. location
   4. cost 5. other
3. Considering the way you learn best, how helpful do you find the following approaches to CME?*
   1. Traditional CME conference (lecture/slide format)
   2. Seminar with emphasis on discussion among peers
   3. Workshops with "hands on" clinical experience
   4. Panel discussion
   5. Self-study material that may be studied at your convenience
   6. Movies/video tapes
   7. Research paper
   8. Small conference (20-40 participants)
   9. Large conference (40 or more participants)
   10. Other (please explain) _____
4. In addition to their educational function, CME meetings may have a social political function. Please indicate how important the following aspects are for you:*
   1. Colleague interaction (peer support)
   2. Medical politics
   3. General relaxation
   4. Resort facilities
   5. Other _____
5. Where would you prefer to attend CME sponsored by the UNM School of Medicine?*
   1. UNM School of Medicine or other location in Albuquerque
   2. Your town
   3. Nearby center (e.g., Raton, Las Cruces, etc.)
   4. New Mexico resort (please specify) _____
   5. Other (please specify) _____
6. Please indicate which month(s) would be the best time for you to leave your practice to attend CME.
7. Please indicate which day(s) would be the best time for you to leave your practice to attend CME.
8. Please indicate the optimum number of days you can spend to attend CME (not including travel time).
9. Please list CME topics you would like to see the UNM School of Medicine present:
   _____ _____
   _____ _____

*On a 1 to 6 Likert scale.

TABLE 2.—*The Most Important Reasons for Choosing CME Programs: % by Specialty (N=410)*

Specialty	Topic	Time of Year	Location	Cost
Family Practice	86	34	83	50
Internal Medicine	85	31	63	32
Pediatrics	92	36	80	54
Surgery	81	27	60	27
Obstetrics/Gynecology	80	52	80	33
Orthopaedics	80	23	61	15
Radiology	96	36	64	20
Emergency Medicine	100	35	64	45
Psychiatry	82	29	82	65

TABLE 3.—*Considering the Way You Learn Best, How Helpful Do You Find the Following Approaches to CME: % of Total Respondents (N=469)*

Learning Format	Not Helpful	Neutral	Very Helpful	No Response
Traditional slide/lecture	5	48	43	4
Seminar	11	40	42	7
Workshop with hands-on	9	30	51	10
Panel	18	55	20	7
Self-study	22	39	32	7
AV	25	49	20	6
Research papers	52	31	7	10
Teleconferencing	57	25	10	8
Small conferences	6	41	44	9
Large conferences	21	52	17	10

ary for CME programs. Pediatricians and emergency medicine physicians preferred the summer months; internists and surgeons indicated winter months other than December or January as most preferable. Friday, Saturday and Sunday were considered the best days. A conference lasting two to three days was felt to be optimum by most respondents.

Discussion

Results of this survey had obvious policymaking implications for the University of New Mexico School of Medicine. In addition, they provided feedback to departments and the OCPE.

One of the criticisms of CME programs is that the traditional educational format is often less than inspiring. It was interesting, therefore, that nearly half the respondents indicated a preference for the traditional lecture and slide format. It is debatable whether this is a well-grounded preference or the result of a lack of exposure of the physicians surveyed to alternative learning styles. In addition, most effective learning styles may differ from preferred learning styles.[6] Active learning experiences such as workshops and seminars emerged as very rewarding learning approaches. Passive learning modalities such as panels, research papers and audiovisual formats were considered less helpful by respondents. When asked about the potential of teleconferencing, which is now being used in many CME programs, most felt it would not be very helpful or, at best, felt neutral about this method. Small conferences were clearly preferred over large meetings.

Of particular interest to respondents were technically oriented short courses. These short courses, which emphasize an experiential rather than lecture format, have been designed to be held locally or at the university's School of Medicine. The most popular of these courses has been the week-long "mini-residency," in which practicing physicians design their own experiences at the School of Medicine. Also, there are reasons besides education for physicians to attend CME activities: relaxation and interaction with colleagues should be facilitated.

It is important for future planning to determine where physicians practicing outside of Albuquerque, the state's largest city, would prefer to attend CME programs sponsored by the University of New Mexico School of Medicine. Nearly half felt it would be highly desirable to come into Albuquerque to attend courses. About 53 percent asked for courses to be held locally; however, this runs counter to expressed desires for interaction with colleagues and relaxation away from daily practice. Considering the data, a mixture of courses held both locally and at the School of Medicine would be most desirable.

Several questions dealt with marketing data designed to help determine the best length of meetings, time of year and days of the week. In all specialties, physicians felt that the optimal meeting would begin on a Friday, last two or three days and be held at various times of the year except for December and January.

While specific topics are too numerous to describe in this paper, 112 separate topics were suggested by the 469 respondents as desirable for CME offered by the medical school.

We attribute the 72.4 percent return rate to several factors. The questionnaires were mailed first-class and addressed to individual physicians. A cover letter was included, personally signed by the Assistant Dean and department Chairs. These physician-administrators were in the position to make decisions based on the information supplied by respondents. The format of the questionnaire was a small booklet with questions that were relevant and easy to answer. Questions were both scaled (on a 1 to 6 Likert scale) and open-ended; comments were allowed at appropriate intervals. The survey was field tested to clarify possibly confusing questions and to determine the time needed for completion. The 15 physicians selected for the field test were typical of our larger sample and were accustomed to having an open dialogue with the School of Medicine. Finally, all responses were confidential.

Conclusion

The information learned from this needs assessment will enable the OCPE to work effectively with both the School of Medicine's faculty and the physicians practicing throughout the state. Because of the thoroughness of the study and its emphasis on marketing data, the faculty have become more willing to rely on the Office of CME to plan and implement their programs. By being responsive to what our state's practicing physicians want, we can provide more relevant, effective CME. In response to their request for self-study courses, we are developing individual learning packets. We are increasing the number of outreach programs to underserved areas to meet that expressed need. We plan to incorporate a variety of educational formats in different environmental settings for our CME programs, and offer numerous smaller courses for clinical participation as a result of the needs assessment reponses on learning styles. The results of the survey will be used by the New Mexico Medical Society and other medical education providers for use in planning their CME programs.

Both teachers and learners often become wedded to a subject-centered approach to education. The needs assessment is a continuous process of communication providing an avenue to develop a learner-centered approach to continuing medical education.

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Health Care Delivery

Costs of Care Provided by Trainees in Internal Medicine and Family Practice

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Most adult patients currently receive their primary health care from family practitioners or internists. What impact this choice has had is not clear. In the past, comparisons have been made between care provided by internists and family practitioners. Using encounter data from the National Ambulatory Medical Care Survey,[1] Noren and co-workers were able to derive the average percentage of visits that generated laboratory and x-ray examinations. Of the internist visits, 73 percent generated laboratory studies, as compared with 34 percent of family practice visits. Internists spent on the average about five minutes longer with each patient.

Joel H. Merenstein, MD, Director of Research at St Margaret Memorial Hospital of Pittsburgh, reviewed charts from the offices of recently trained, board-certified, family practitioners and general internists practicing in southwestern Pennsylvania. Internists were found to order an average of 1.1 laboratory or x-ray tests per visit compared with 0.58 for the family practitioners (written communication, August 13, 1981). Nearly half of the internists' dispositions indicated that the patients should return for another scheduled visit. Over twice as many of the family practice visits ended without a specific return-appointment date. The referral rates were similar.

Smith and McWhinney[2] compared practice habits of internists and family practitioners using "programmed patients" (research assistants who gave predetermined answers to questions). The authors concluded that though there was no difference in the final diagnosis reached, the family practitioners asked fewer history questions, requested fewer items of data about the physical examination and ordered fewer laboratory investigations.

All of these studies have used either study populations or techniques that might tend to bias the results. Studying actual practices may present significant selection bias and skew the results. The use of sham or programmed patients would seem to solve this problem but enters the bias of an artificial test situation. A physician tends to respond with the answer he or she feels is expected, rather than follow the procedure that would be used in the office. The fallacy of this form of testing was demonstrated by Rose and colleagues,[3] who showed that internal medicine residents who responded on a test that certain routine screening procedures were indicated did not carry out or order these same tests in their actual practice.

To understand the differences in ordering and referral habits of family practitioners and internists, we randomly assigned new clinic patients to internal medicine or family practice trainees. In this way we were able to eliminate the self-selection biases of previous studies.

Methods

The University of California, Davis has family practice and internal medicine training programs. Each program runs a separate primary care outpatient clinic. The attending staff in the internal medicine clinic are full-time and community-based internists. The family practice clinic uses full-time and community-based family practitioners. New patients enter the system either from hospital discharge, emergency room or acute care clinic referrals or through self-referral. There is little or no formal communication between the two clinics; therefore, separate procedures are used for making appointments in each of the clinics.

During the randomization period, each patient who called for a new appointment was asked if he or she would object to being seen in either clinic. The charts of those patients having no objections were then reviewed by members of the faculty. Any patient who would not

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normally be an acceptable patient to either clinic was removed from the study (for example, obstetric and pediatric patients were not included in the study). Patients who had not previously been seen in either clinic and were acceptable as new patients to both clinics were then randomly assigned to one of the clinics and informed of their appointment time. Neither the patients nor the providers were aware that their charts were going to be retrospectively reviewed.

About seven months after the randomization, all of the charts were pulled and reviewed. A five-month period of time after the initial visit was examined. Charts were reviewed and evaluated for frequency of visits, laboratory studies ordered, number of referrals, acute care clinic visits, emergency room visits, hospital admission and form of follow-up. To verify adequate randomization, they were also compared for age, sex and race.

Results

In all, 100 patients were randomly assigned, 50 to each clinic. Eventually 27 patients were seen in each clinic. Using a chi-square analysis, no statistical difference was found in the age, race or sex of the patients assigned to either clinic.

A chi-square analysis of all the laboratory tests used in each clinic failed to show any significant differences. The total costs of laboratory tests per patient were compared. The average cost of laboratory tests per patient in the internal medicine clinic was \$117.96 (SD = 119.44). The average cost in the family practice clinic was \$113.40 (SD = 146.04).

To compare total cost of ambulatory care provided, a comparison of clinic visits, acute care visits (the nonacute emergency room) and consultations was carried out. The distribution of visits is outlined in Table 1. A chi-square analysis of these figures showed no significant difference. If prices are assigned to each visit, a total cost of physician care can be derived. The average cost for each type of visit was used to compute the total average expenditure per patient. The average cost of physician care over the five-month period, not including laboratory tests, was \$167.89 (SD = 102.23) in the internal medicine clinic and \$194.61 (SD = 144.37) in the family practice clinic. Using a Student's *t* test, this \$26.72 difference did not reach statistical significance.

The total cost of ambulatory care, physician and laboratory costs, not including pharmacy and other ancillary services, was \$288.43 (SD = 206.22) in internal medicine and \$306.73 (SD = 248.00) in family practice. This represents a statistically insignificant difference using a Student's *t* test. It is important to realize

TABLE 1.—*Patient Visits of 54 Patients During a Five Month Period*

	Internal Medicine (No. of Patients = 27)	*Family Practice (No. of Patients = 27)*
Clinic	60	65
Acute care	6	5
Consultations	12	15

that the sample sizes were small; large differences would have had to be present to show significance. To reach significance at a level of $P = .05$ with the sample sizes and standard deviation used, the difference in laboratory costs would have had to be \$70.81 and the total costs would have had to differ by \$132.29. Looked at in another fashion, for this small difference in cost to have been significant we would have needed a population of 7,881 patients for our study.

Conclusion

Selection bias has apparently played a significant role in previous efforts to compare practice costs and habits of internists and family practitioners. Unless the population of patients seen by the practitioners is randomly selected, it is of little value to compare the care provided. In this small randomized study it was shown that the cost of care was not significantly different between the two training sites. In previous studies, authors have often suggested that family practitioners order fewer laboratory tests. The difference in the cost of laboratory tests ordered in this study was less than 4 percent of the total cost of laboratory tests. The total cost difference for five months of ambulatory care by internists or family practitioners was 6 percent.

Because of the small sample size and the large standard deviations, it would be inappropriate to conclude that there is no difference in the cost of care provided by internists or family practitioners. However, even with these small numbers, the 50 percent differences reported by other authors would have reached significance. The study makes one look with suspicion upon nonrandomized studies that report large differences in the costs of care. Further large-scale randomized studies should be conducted in the near future. While we await the results of these studies it is premature to make long-term political, social and educational decisions about the direction of future primary health care based on the available data.

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The 'Request for Proposal' Approach to Designation of a Trauma Center

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Although much has been written about the need for trauma centers, little has been published concerning the method of designating one. The New Mexico Emergency Medical Service Bureau of the Health and Environment Department invited all hospitals in the region to submit a Request for Proposal (RFP) to be designated the trauma center for that region. A selection committee made up of two trauma surgeons and an emergency physician reviewed the RFP documents and visited each competing hospital. The selection committee's report was presented to the New Mexico Medical Society in an open forum. The Emergency Medical Service Bureau reviewed both the report and the response of the medical society, which was supportive. Finally, a designation was made by the bureau and announced by the governor, and was well accepted by all of the participating parties.

The primary responsibility for the establishment of a regional trauma plan and the designation of a regional trauma center was vested in the New Mexico Emergency Medical Services (EMS) Bureau, the lead agency, and its medical director, an emergency physician. The process used involved other emergency physicians and included input from the local medical community. However, without governmental and individual commitment, the improved organization of prehospital and hospital care for multisystems-injured patients would have been derailed by a number of private interests. It is the purpose of this paper to share the experience of one community in its approach to the designation of a regional trauma center.

Lead Agency Commitment

The EMS Bureau was committed to a regional trauma plan for some fundamental reasons. First, trauma is a major health problem. It is the leading cause of death in persons younger than 40 and the leading source of worker's compensation and disability.[1] Trauma is the third leading cause of death in the population at large, both nationally and in New Mexico.[1,2]

Second, the advances in the care of civilian multiple-trauma patients in regions with trauma centers were appreciated. Many salvageable trauma patients die from irreversible shock or its complications. Early supportive care and definitive treatment reduce the incidence of irreversible shock (Figure 1). Civilian communities with regional trauma systems that utilize local medical resources to the fullest have dramatically reduced their death rates.[3-7] These noble goals were adopted by the EMS Bureau to be implemented in New Mexico.

Because the leadership and overall responsibility for the care of multiple-trauma patients generally emanate from a regional trauma center, early recognition of that site enhances its authority during the later development and implementation of a regional trauma plan. It is important from the beginning to identify the resources available for the care of patients and to know the destination of patient referrals so transport systems can be arranged. With these facts in mind, it became evident that the first step in the development of a regional trauma plan was the designation of a trauma center. The particular process used accomplished these initial goals.

Refer to: Bova CM: The 'Request for Proposal' approach to designation of a trauma center (Health Care Delivery). West J Med 1983 Jan; 138:120-125.

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ABBREVIATIONS USED IN TEXT

EMS=Emergency Medical Service Bureau (New Mexico Health and Environment Department)
RFP=Request for Proposal

Definition of Request for Proposal

Request for Proposal (RFP) is a competitive bidding process that is open and equitable. Hospital administrators are familiar with the RFP process and recognize it as a fair method for making a politically sensitive choice. When a regional trauma center is designated, the RFP becomes a contractual agreement by that hospital to the emergency medical services lead agency to provide the personnel, facilities and services proposed. All hospitals in the region were invited to compete for designation as the regional trauma center by submitting a proposal defining their personnel, facilities, organization and degree of commitment. Some hospitals competed for trauma center designation for economic, prestige and service-oriented reasons. Other hospitals were eliminated naturally during the self-evaluation process of committing on paper their resources and interest in becoming a regional trauma center.

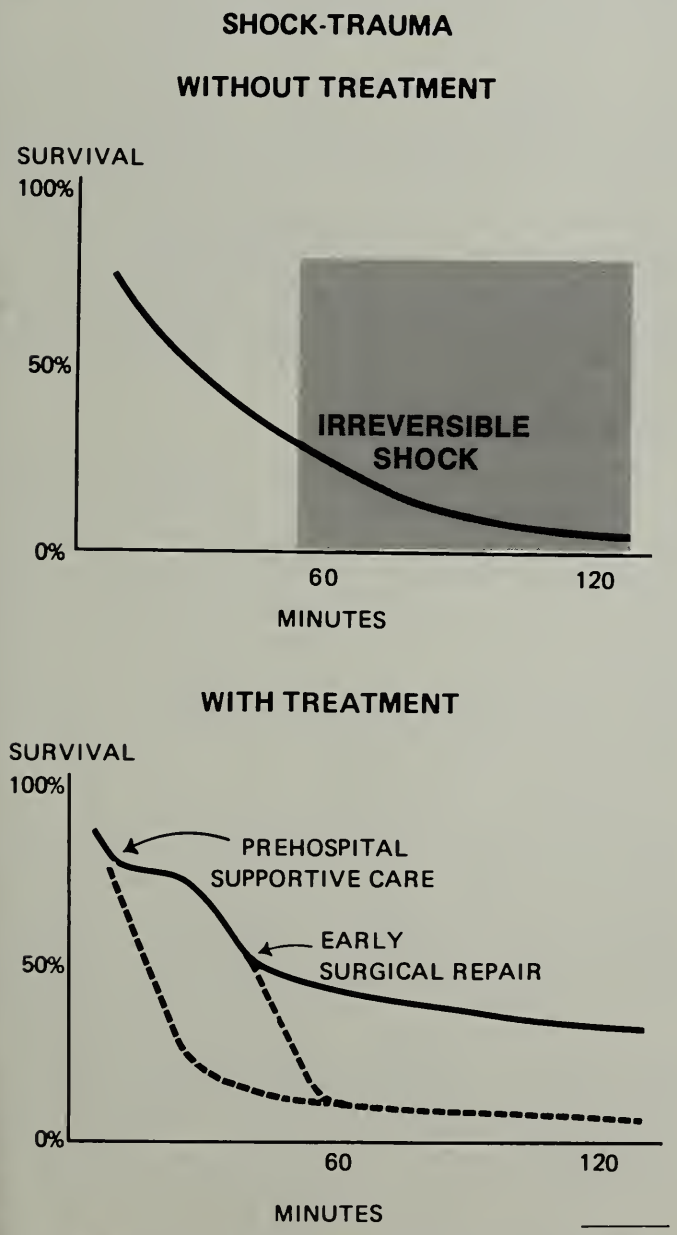

Figure 1.—The effects of early treatment on mortality.

Criteria

The EMS Bureau drafted requirements for a Request for Proposal using the national standards developed by the American College of Surgeons Committee on Trauma.[8,9] The maintenance of national standards was considered important because it enables a region to compare its outcomes and statistics with those of other regions. It was also thought important that a level I center in Albuquerque have the same implications as a level I center in Orange County, California, for example. This was not to imply that a regional trauma center had to be level I. Most communities do not have the resources, manpower and treatment needs for a level I facility. However, every region should have a regional trauma center (level I, II or III) where the available resources are used fully for improved standards of care.

In addition to the American College of Surgeons' standards, there were other items included in each RFP. Two narratives were required of each hospital to help evaluate its potential as a trauma center. The first narrative asked for a description of the administrative hierarchy of the proposed facility, clearly delineating the authority of the trauma service medical director. This authority is crucial if a trauma service is to have equal priority with radiology, laboratory services and so forth, which is essential to provide care for the seriously injured in a timely manner. The second narrative asked for a description of a fictitious multiple-trauma patient's care from the prehospital phase through the emergency room to the operating room and intensive care unit. This was needed to outline patient flow and the trauma service's role at each of these clinical stages. In the RFP the hospital was asked to quantitate and qualitate its facilities (that is, number of intensive care unit beds and the like) and their personnel (for instance, number of board-certified surgeons).

Financial expectations were to be addressed in the RFP. Any grants or funding that the EMS Bureau needed to appropriate to the trauma center were indicated, and the trauma center was asked to agree to care for all trauma patients from that region regardless of their ability to pay. Medical control of prehospital treatment, medical education, public relations, data collection and evaluation of the trauma service were also to be addressed.

The draft of the RFP requirements was then reviewed by a criteria committee consisting of representatives with expertise in trauma or emergency medical services from the regional hospitals, the medical society and the hospital association. The purpose of this committee was threefold. First, the RFP must be thoroughly under-

stood by the participating hospitals. All ambiguities were discussed and removed. Second, the committee wanted to upgrade the national standards when local resources were available to do so. For example, the American College of Surgeons' requirements for in-hospital general surgery coverage could be fulfilled by physicians in residency. The local committee chose to define the postgraduate year of such residents and required in writing that the trauma service medical director attest to the residents' competence. Thus the immediate surgical capability of the trauma center was preserved when residents fulfilled the in-house requirements. Third, this committee helped educate and prepare the medical community for the designation of a regional trauma center.

Six weeks were allowed for the hospitals to complete the RFP. It was during this time that protests were made through the medical society to the lead agency to rescind the designation process. Delays were granted and hearings begun in an attempt to improve the understanding and acceptance of a regional trauma plan. It was important to gain acceptance from the local medical community if the program was to be implemented and used. Although regional trauma plans and centers are the national trend, they may not be so recognized by local experts for varied reasons.

The question of the need for a regional trauma center was raised by the medical society. To answer that, they investigated the absolute number of emergency room visits, hospital admissions and emergency-room-to-surgery cases of trauma. This study cost the hospitals involved a total of $8,000. However, several estimates proved to be remarkably close to the absolute number of serious multiple-systems injured patients as defined by the medical society's study. The use of these formulas is recommended as a savings of time and money.

The medical society's study identified 3,500 hospital admissions for trauma, of which 525 (15 percent) were serious enough to require immediate surgical intervention. The Trunkey formula,[10] which is based on motor vehicle accident statistics available from the New Mexico Department of Transportation, gave an estimated 435 critical trauma patients for this same area. This underestimate was felt to be related to the prevalence of penetrating injuries such as gunshot or knife wounds and the formula could be adjusted to take that into account (Figure 2).

Another estimate was based on a population formula: one serious multiple-trauma case per 1,000 population (Figure 2). This estimate gave 498 patients for the same area, which was close to the absolute figure of 525. Even though these estimates are useful for developing a regional trauma plan, that planning should take place without regard to the exact number of injured so that available resources are enhanced and utilized efficiently.

During the controversial hearings that ensued, the designation process was at that point most vulnerable. The authority to pursue this project needed to be secure

TRUNKEY FORMULA

Number of critical trauma patients = Number of MVA fatalities + 5% of MVA injuries

IN THE ALBUQUERQUE AREA

134 MVA fatalities in 1979
+ 301 = 5% of 6,666 MVA injuries
435 = Number of critical trauma patients

POPULATION FORMULA

Number of serious multi-trauma patients = 1 per 1,000 population

IN THE ALBUQUERQUE AREA

498,000 population = 498 serious multiple trauma patients

Figure 2.—Two methods of estimating the number of patients per year with critical trauma (Trunkey Formula from Teufel and Trunkey[10]). MVA = motor vehicle accidents.

as the date for a decision approached. The EMS Bureau kept its superiors well informed of all controversy and did not become immobilized by the protests. The bureau reset the deadline for the participating hospitals to submit their RFP's while indicating that the regional resources had to be identified before there could be any further debate over the merits of a regional trauma plan and center. When one hospital submitted an RFP application, the others did likewise, not wanting to risk being left out of the selection.

The Selection Committee

As the RFP's were submitted, a selection committee was formed. There were several questions the committee members were asked to consider objectively before making recommendations to the EMS Bureau. It must be emphasized that this committee acted only in an advisory capacity to the bureau, which had the final authority to designate the regional trauma center. However, the members' opinions were carefully considered as the bureau made the designation, and they definitely added weight to the decision.

The selection committee was used to settle the smoldering controversies that the designation process had raised. Some of the questions effectively answered were as follows: Is there a sufficient volume of trauma in the region to justify a trauma plan and center, and why? Which hospital and staff would best serve the area if designated the region's trauma center, and why? Based on the American College of Surgeons' categorization, what is the level of each hospital seeking the designation, and why? Finally, how will the designation of a trauma center and the development of a regional trauma plan improve the care of multiply injured patients in the urban and rural parts of the region? The selection committee had a different function from the American College of Surgeons' Verification Committee, which

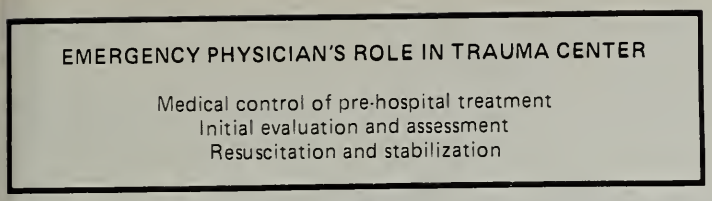

Figure 3

acts to categorize the level of a hospital previously designated the region's trauma center.[11]

Choosing the Committee

A nationwide search was conducted for two trauma surgeons and an emergency physician to serve on the selection committee. The chairmen of the committees on trauma of the American College of Surgeons and the American College of Emergency Physicians were contacted for appropriate names. The final choices were based on national prestige, orientation to the concept, experience in this role and availability. R. Adams Cowley, MD, from the Maryland Institute of Emergency Medical Services and Systems; Kenneth L. Mattox, MD, from the Baylor College of Medicine, Houston, and John C. Sacra, MD, the Director of Emergency Medicine at St Francis Hospital, Tulsa, Oklahoma, performed exceptionally well as the members of the selection committee.

The advantage of having an emergency physician on the selection committee can be easily understood when one views his or her function in a regional trauma plan. Emergency physicians are the link between prehospital and hospital care. Medical control of prehospital treatment in most systems is the responsibility of emergency physicians. They are involved with "off-line" medical protocols, "on-line" radio and telemetry communication and quality-assurance activities such as audits and case reviews to ensure that the prehospital treatment is appropriate and accountable. Emergency physicians are involved in the total emergency medical services system in which trauma is one of the more frequent, but not exclusively so, life-threatening emergencies (Figure 3). With trauma, an emergency physician's expertise is in the initial evaluation and resuscitation of a patient.[12] As long as a patient's needs are kept in focus, and not the physician's, emergency physicians and trauma surgeons can complement each other's activities as more than one pair of hands is needed to rapidly stabilize and prepare a patient for surgical intervention. The chain of command and communications between these specialists should be defined at the local level.

Therefore, the emergency physician's assessment of the prehospital system, the emergency department, the initial evaluation and resuscitation of patients and communication between the emergency physicians and surgeons was a valuable asset to the selection committee. The value of trauma surgeons as members of the selection committee needs no further elaboration.

On-Site Visits

Before their on-site visits, the selection committee reviewed the RFP of each hospital, plus geographic and demographic materials. At an orientation, they were informed of the lead agency's authority to designate the trauma center. They were apprised of the heated local issues that would arise during the visits, and responses to the news media's inquiries were offered.

During the on-site visits, four hours were allowed for each hospital. It was the hospital's responsibility to schedule that time. The personnel, facilities and meetings planned helped define their awareness and commitment as a trauma center. The lead agency supplied a scoring sheet that helped the committee be objective (Figure 4). The scoring sheet weighed four areas of that institution for suitability as a trauma center: hospital categorization by American College of Surgeons standards, the dedicated trauma service, administration and management, and allied and support programs. The on-site evaluation worksheet (Figure 4) is a revision of the one used in Albuquerque. This revision was based on a communication (memorandum, February 17, 1981) from Edward D. Martin, MD, Assistant Surgeon General, to regional EMS directors, received after the selection process was completed. As previously mentioned, the worksheet was used to ensure the objectivity of the selection committee. It defines and ranks a number of important components of a trauma center to be evaluated during the selection process. The weight of these components expressed the bias of the author and is intended to be a guide for other regions in establishing their own scoring formula. Furthermore, the worksheet becomes a permanent public record of the evaluation, which may be helpful if there are objections, protests or litigation surrounding the selection process.

At the conclusion of the on-site visits, the selection committee formed a consensus based on the RFP's and visits. Their recommendations were reviewed with the EMS Bureau and presented to the medical society on the final day. This open forum was beneficial in unifying a divided community concerned about regional trauma care.

The EMS Bureau was pleased to receive an endorsement of the selection committee's recommendations by the medical society. The seemingly endless debate over the designation was worth it as a regional trauma plan was now understood, accepted and supported. Before the final announcement was made, there was one more important step. The EMS Bureau's staff met with the designated hospital's administration and trauma service medical director to conclude a written agreement and establish a working relationship. The deficiencies to be improved and all responsibilities were clearly outlined to ensure that optimal care would be provided for multiple-trauma patients in the region.

Final Choice

Finally, after eight months of work by the EMS Bureau, Governor Bruce King designated the University of New Mexico Hospital as the trauma center for

northern New Mexico. The announcement explained the need for and projected impact of a trauma center on the care of all critically injured patients. Emergency services at the other regional hospitals are to be continued for minor trauma, traditional physician-to-physician referrals and disaster management. For the university, the designation is only the first step in the challenge of being a trauma center. They have the responsibility, vested by the EMS Bureau and supported by the medical society, to make trauma a manageable

TRAUMA CENTER SELECTION

Hospital _____

		Maximum Points	Points
I.	**HOSPITAL CATEGORIZATION BY A.C.S. STANDARDS - 25%**		
	A. Personnel (quality, quantity, availability)	10	_____
	B. Facilities (equipment, layout)	10	_____
	C. Commitment of hospital	10	_____
	TOTAL	30	_____
	Comments.		
II.	**THE DEDICATED TRAUMA SERVICE - 33.3%**		
	A. Chief of Service (authority, leadership, experience)	10	_____
	B. Prehospital Medical Control (transfer agreements, treatment, triage, and operational protocols, direct medical control, quality assurance activities)	10	_____
	C. Patient Flow Within Trauma Center (ER to OR to ICU, etc.)	10	_____
	D. Quality Assurance (Trauma registry, mortality/ morbidity conference, audits, autopsy studies)	10	_____
	TOTAL	40	_____
	Comments.		
III.	**ADMINISTRATION AND MANAGEMENT - 16.6%**		
	A. Authority and Hierarchy in Center	10	_____
	B. Financial Planning and Development	10	_____
	TOTAL	20	_____
	Comments:		
IV.	**ALLIED AND SUPPORT ACTIVITIES - 25%**		
	A. Training (First responders, EMTs/paramedics, nurses, physicians both inside and outside Center)	10	_____
	B. Public Relations Program	10	_____
	C. Research Activities	10	_____
	TOTAL	30	_____
	Comments:		
	GRAND TOTAL	120	_____

_____
Name of Selection Committee Member

Figure 4.—Worksheet to be used at on-site visits by trauma center selection committee. ACS = American College of Surgeons, ER = emergency room, OR = operating room, ICU = intensive care unit, EMT's = emergency medical technicians.

and treatable disorder in northern New Mexico. Both the labor and rewards of that task are yet to come.

Conclusion

It is appropriate for the emergency medical services lead agency to designate regional trauma centers. The RFP approach for that selection is a competitive bidding process that is equitable and helps identify local resources. Emergency physicians have a valuable perspective and contribution to make in this area of emergency medical services system development. Multiple-trauma patients will benefit from an organized, predetermined system of care that utilizes local resources.[1-8,13,14] The RFP designation process makes this possible through competition.

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Book Reviews

The Western Journal of Medicine *does not review all books sent by publishers, although information about new books received is printed elsewhere in the journal as space permits. Prices quoted are those given by the publishers.*

VITAMINS AND 'HEALTH' FOODS: The Great American Hustle—Victor Herbert, MD, JD, Professor of Medicine, State University of New York, Downstate Medical Center, Chief, Hematology and Nutrition Laboratory, Bronx VA Medical Center, and Stephen Barrett, MD, Chairman, Board of Directors, Lehigh Valley Committee Against Health Fraud, Inc. George F. Stickley Company, 210 West Washington Square, Philadelphia, PA 19106, 1981. 189 pages, $11.95.

This is the latest in a series of books on health fakery and quackery, edited by America's prime quack-kicker, Stephen Barrett, MD. This one is written by Victor Herbert, MD, JD, professor of medicine at New York University. His knowledge of nutrition quackery is encyclopedic.

The book is an up-to-date exposé of so-called "health food" quacks, their organizations, marketing techniques and economic and political methods of bamboozling the public while staying just within the law, and sometimes outside of it.

Herbert and Barrett present the misrepresentation of vitamins and so-called health foods and supplements as a serious national problem. There seems to be no field wherein so much misinformation has so much public tolerance.

They present many hard-hitting facts. For instance, Shaklee, of the food products company, was a chiropractor. He and his two sons owned $62 million in stock in their company as of 1980. Herbert discusses the company's marketing techniques. Robert Atkins, MD, (the Atkins' Diet), is said to promote vitamins as being more effective than medications against disease. "Dr" Carlton Frederick (not his real name) has a degree in communication and no significant training in nutrition. Yet, he is worshipped as America's number one nutrition authority and was once convicted of practicing medicine without a license. The list goes on and on.

Herbert shows how the National Nutritional Foods Association advises "health food" store proprietors on avoiding Food and Drug Administration regulations on false labeling; how to give nutritional advice without appearing to prescribe; how to get on radio and TV.

Another chapter records illogical and unscientific court and administrative rulings that allow hustling to exist. There is a good section on the dispute over the concept of the terms "organic" and "natural."

There are some defects. For instance, there are five references to "vitamin B_{15}," decrying its fraudulent promotion and inconstant contents, but no mention of what its main ingredients usually are (dimethylglycine or dichloroacetate, or both, plus inert materials). Several chapters contain passages taken from Barrett's prior publications—especially *The Health Robbers* (without credits), but there is also updated material that makes the reading worthwhile.

Herbert's previous book *Nutrition Cultism* is a more complete and technical review of clinical and biochemical information. Together with this volume, they make a good pair. Any physician whose patients may be involved in nutrition cults should have these two books for reference. Also buy a copy and donate it to your public library.

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SPORTS MEDICINE: Fitness, Training, Injury—Edited by Otto Appenzeller, MD, PhD, and Ruth Atkinson, MD. Urban & Schwarzenberg, Inc., 7 East Redwood St., Baltimore, MD 21202, 1981. 395 pages, 119 illustrations, $39.50.

This book was written for medical students enrolled in the sports medicine course at the University of New Mexico School of Medicine. As a text it touches on the entire field of "sports medicine" from exercise physiology to injury management but in a manner obviously designed to support lectures. The sections on the nervous system, nutrition, hormones, fluids and electrolytes, and exercise physiology are well documented literature reviews. Unfortunately most of the authors fail to place the reviewed material in perspective and thus the reader is left with bits and pieces and the task of looking up the references—fine for students but perhaps unrealistic for practicing physicians.

The two chapters (temperature regulation and nutrition) written by the editors are excellent. Not only is the literature thoroughly reviewed but the information is collated into a readable narrative form.

The final section (injuries and locomotion) deals primarily with athletic trauma. Although this section touches on all of the injuries that might occur in sports, those problems that occur on a daily basis are given little more attention than those seen once in a lifetime. In addition there is scant attention paid to the sports-specific injuries that are often the most troublesome to diagnose and manage.

The need for aggressive and knowledgeable rehabilitation is the primary difference between managing athletic injuries and managing garden variety soft tissue trauma. For physicians seeking guidance in this area the book will be of little help. Although the descriptions of diagnostic techniques are somewhat more complete they are still inadequate for a physician not already familiar with the performance of these various tests.

The book would be a good investment for two groups of persons: medical students and practicing physicians desiring a relatively current literature review of those aspects of sports medicine not related to injuries. For physicians seeking assistance in diagnosing athletic injuries or in formulating treatment programs, it offers little.

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DRUGS DURING PREGNANCY: Clinical Perspectives—Raja W. Abdul-Karim, MD; with contributions by Howard J. Osofsky, MD, PhD; Donald R. Mattison, MD, and Roger Scott, JD. George F. Stickley Company, 210 West Washington Square, Philadelphia, PA 19106, 1981. 152 pages, $15.00.

The thalidomide disaster and the recognition that a number of other drugs such as diphenylhydantoin and sodium warfarin may be human teratogens have emphasized the potential risk of medications in pregnant women. The dilemma is confounded by the fact that the effects of some drugs may not be apparent until years after they are prescribed—for example, the consequences of diethylstilbestrol. Our knowledge of these risks is far from complete and what information there is has often been difficult to obtain. How many of us have been frustrated when using the *PDR* and finding the statement, "The safe use of this medication in pregnancy has not been established"? In order to evaluate the risks of medications one must not only have an understanding of teratology and principles of drug transfer, but must also have an appreciation for the pitfalls inherent in this type of research. Dr Abdul-Karim has undertaken an ambitious project in his book *Drugs During Pregnancy—Clinical Perspectives.* Several chapters are devoted to instruction in basic principles of drug transfer and teratology. Approximately half of the book is devoted to discussion of specific medications and an assessment of their influence on pregnancy outcome. There is a chapter on the mechanisms of drug toxicity and a discussion of reproductive toxins with num-

erous examples, including environmental agents and their influence on reproduction. The book is very readable and provides sufficient background information for those who must deal with these problems.

One may be called upon to obtain information regarding drugs in pregnancy for either of two general purposes. One may wish to prescribe a drug to a patient for a given indication. Frequently, there is more than one suitable drug. An example is a patient who is hypertensive and needs antihypertensive medication. In this instance, the practitioner wishes to find a drug that will be effective in pregnancy and pose the least risk to the mother and fetus. The second reason for desiring information concerning a drug in pregnancy is to counsel patients regarding the risks of drugs that they have already taken or are presently using. *Drugs in Pregnancy—Clinical Perspectives* would serve the first purpose well but would not be as helpful for the second. This book discusses somewhat over 60 medications and their influence on pregnancy outcome. The medications are discussed by class of drug: anticonvulsants, anticoagulants, antibiotics and so forth.

A number of drugs are conspicuously absent. There is no mention of acetaminophen, metronidazole or sodium warfarin, to mention just a few. It was apparently not the intent of the author to provide a comprehensive discussion of drugs but rather to provide background information and appropriate examples. Another recently published book entitled *Handbook for Prescribing Medications During Pregnancy* by Burkowitz, Coustan and Mochizuki (Little, Brown, and Company, Boston, 1981) lists twice as many drugs and is a very helpful, quick reference book. It, however, has none of the background information of Abdul-Karim's text. I believe that both of these publications should be on the bookshelf of everyone providing care to pregnant women. Though there is some duplication, the books complement each other well.

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MEDICO-LEGAL IMPLICATIONS OF DEATH AND DYING—David W. Meyers. The Lawyers Co-operative Publishing Company, Rochester, NY 14694, and Bancroft-Whitney Company, San Francisco, CA 94107, 1981. 639 pages, $65.00.

Mr Meyers makes an outstanding contribution to both the medical and legal professions in this latest publication (1981), dealing with a broad range of subjects that regularly are of compelling interest and concern to physicians as well as attorneys.

In treating in-depth topics such as dying, informed consent, standard of care owed to dying patients, orders not to resuscitate and terminating lifesaving treatment for hopeless patients, Mr Meyers confronts directly many of the vexing issues that daily translate into some definitive, discreet action by practicing physicians. The chapters on informed consent and orders not to resuscitate are particularly strong because, in addition to a thorough and lucid discussion of the applicable law and cases, they contain specific instructional protocols that should prove highly useful to medical staffs utilizing them as advisory standards and suggestions. The personal opinions expressed by the author are concise, scholarly and well-buttressed by legal principle and case law. In the sections on terminating lifesaving treatments for hopeless patients, the method for presenting in sequential fashion detailed analyses of pertinent cases such as Quinlan, Eichler and several Massachusetts cases is particularly useful and illuminating in deciphering these parts of the law. By adding those chapters that deal with ethical and religious considerations, Mr Meyers adds a commendable dimension to his efforts, serving to strengthen the entire work.

Although the title *Medico-Legal Implications of Death and Dying* is an appropriate one, there are exceedingly useful discussions on related topics, such as informed consent, that exceed the boundaries suggested by the book's title.

The volume is well constructed, with good print, and the exposition is nicely organized, thoroughly annotated and written in refreshingly readable language.

This work, in my opinion, is a very significant addition to our knowledge in this general area. It properly deserves a place in every practicing physician's collection as well as in all medical and legal libraries.

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MNEMONICS, RHETORIC AND POETICS FOR MEDICS—Robert L. Bloomfield, MD, and E. Ted Chandler, MD, Department of Medicine, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, NC. Harbinger Press, Box 17201, Winston-Salem, NC 27106, 1982. 222 pages, $9.50 (softbound).

Even if Rubik's Cube left you confused, you will enjoy this Bloomfield and Chandler collaboration. Much of medicine is a jumble of facts and associations but these authors have distilled everything from the causes of fecal leukocytes (STUPE) to the signs of spinal compression (SHARP WALL) to *Mnemonics, Rhetoric and Poetics for Medicine* (MRPM).

Where did they find these? There must be at least 100 or more mnemonics in this book. I searched my library and there it was! I found my old blue book which I compiled as a resident and in there were many of these memory aids. I called my book my "Peripheral Brain" and so this new volume must be a compilation of many such books.

Not only are there memory aids in MRPM but medical sense and sensitivity: "One unfortunate aspect of Crohn's disease is the need for surgery in over two-thirds of patients because of fistula formation, obstruction, or abscesses." Then follows the main indications for surgical intervention in inflammatory bowel disease expressed as an acrostic: I CHOP! (Get it?)

Amongst this alphabetic soup runs a thread of judgment, experience and humor. There is still humor in medicine.

This book could make a splendid gift for a beleagured medical student, compulsive resident or a diligent practitioner (BCD). There is one irony: with such parsimony, why such a weighty, unwieldly and awkward title? MRPM makes no SENSE. Now that's a puzzle!

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LUNG DEVELOPMENT: BIOLOGICAL AND CLINICAL PERSPECTIVES—Volume II: NEONATAL RESPIRATORY DISTRESS—Edited by Philip M. Farrell, Department of Pediatrics, University of Wisconsin Clinical Sciences Center, Madison. Academic Press, Inc., Publishers, 111 Fifth Ave., New York, NY 10003, 1982. 307 pages, $37.50.

This book is a multiauthored collection of state of the art chapters about various aspects of the respiratory distress syndrome (RDS) of premature infants. Other subject matters covered include bronchopulmonary dysplasia and brief references to other causes of respiratory distress in infants. The book is the clinical volume of a two-volume set; Volume 1, titled *Biochemistry and Physiology*, will be of interest only to those actively involved in lung-related research. This second volume covers three areas relating to RDS: diagnosis and management of RDS, assessment of fetal lung maturity and prevention of RDS by maternal treatments with corticosteroids. While the book is multiauthored, the style of presentation is consistent throughout and easy to read, and the chapters are complementary and not repetitious. Several chapters should be very useful for any general pediatrician who is occasionally faced with the care of an infant with RDS, while containing sufficient detail and references to maintain the interest of a practicing neonatologist.

Dr Edwards has written a thorough review of the x-ray diagnosis of RDS and related conditions. Drs Gutcher and Perelman use a case study of RDS to illustrate the thought processes used and therapeutic options available to neonatologists when caring for such an infant. This chapter is not a cookbook for care, rather it is a balanced exposition of the various approaches and guidelines that have been published. Drs Tsao and Zachman have written a very thorough and scholarly chapter that analyzes the various tests that have been proposed to assess fetal lung maturation. They have reviewed the results of 10,840

published measurements of lung maturity and score the predictability, sensitivity and specificity reported for the various tests. The final recommendations are that each laboratory must define its own standards and that the L/S ratio is as good as other proposed tests. This extensive summary will be useful to any clinician who uses fetal lung maturity testing. Other chapters may be less useful to clinicians. The excellent chapter by Dr Ballard on hormonal effects during lung development might better have fit into Volume 1 of this series. The chapters on glucocorticoid therapy to prevent RDS are very detailed in their presentation of the National Collaborative Study and are thus of interest primarily to people actively involved in this area. However, the final very balanced recommendations for the use of corticosteroids should be useful as a guideline to practicing obstetricians. In summary, the volume contains a number of excellent up-to-date reviews that present to the reader an overview of a complex area. The book will serve best those seeking a thorough, current perspective of RDS.

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RECENT ADVANCES IN CLINICAL NEUROLOGY—Number Three—Edited by W. B. Matthews, DM, FRCP, and Gilbert H. Glaser, MD, MedScD. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1982. 254 pages, $27.50 (softbound).

Recent Advances in Clinical Neurology, edited by Matthews and Glaser, is an ongoing anthology of current, up-to-date information on important topics in clinical neurology. The first two volumes, which were reviewed previously [West J Med 1980 Nov; 133:460], provided useful guides to a variety of clinical problems. The third volume once again includes a number of well-selected clinical entities of interest to both practicing and academic neurologists. As the editors point out, the authors of the various chapters have taken into account "the increasing application of advanced laboratory science to the problems of clinical neurology." The topics cover a wide area and all have clinical relevance.

An extensive and authoritative chapter, "Defects of the Energy Pathways of Skeletal Muscle," by J. A. Morgan-Hughes appropriately divides muscle diseases into two main categories according to the site of the biochemical lesion—those in which the cell cytosol (the soluble part of the cell cytoplasm) is affected and those disorders that involve the processes of oxidative metabolism within the mitochondria. Within these two major categories of genetically determined muscle disorders, the author subclassifies the diseases according to specific enzymatic defects, defects of substrate transport and utilization, defects of electron transport, and finally defects of energy conservation and transduction. The classification of these diseases is both novel and logical. The chapter contains much of new and clinically valuable information and provides a very complete list of references.

A brief, but concise, chapter on peripheral nerve compression syndromes by A. Downie reviews the major entrapment syndromes, their clinical manifestations and the effective treatment for each.

The chapter "Concepts of Acute Management of Spinal Cord Injury" by W. F. Collins and B. Chehrazi discusses the latest noninvasive and invasive surgical approaches to the treatment of spinal cord injury. Both experimental studies and current clinical concepts are reviewed. The discussion of decompression and reduction of edema as well as correction of altered blood flow to the injured cord segments is very useful.

P. Nathan devotes a chapter to a discussion of "The Anatomy, the Physiology, and the Management of Pain." Included are reviews of endorphins, opiates, acupuncture and electrical stimulation.

A comprehensive and clinically relevant chapter on multiple sclerosis by H. M. Wisniewski, H. Lassman, C. F. Brosnan, P. D. Mehta, A. A. Lidsky and R. E. Madrid considers the latest immunologic and experimental aspects of this disease. Of particular interest is the discussion of the animal model of relapsing and remitting allergic encephalomyelitis that bears resemblance to multiple sclerosis in man.

"The Pathophysiology of Friedreich's Ataxia" by A. Barbeau includes a discussion of some of the latest biochemical research dealing with the aberrations of carbohydrate metabolism thought to underlie this genetically determined disease as well as other forms of hereditary ataxia.

A chapter devoted to various aspects of epilepsy, written by Glaser, includes an up-to-date review of valproic acid and its use in the management of seizures. Epilepsy and the menstrual cycle and the ins and outs of the surgical treatment of temporal lobe epilepsy are reviewed in an authoritative manner. The chapter includes a useful list of references.

A discussion of two interesting pediatric neurological diseases, Reye's syndrome and Sturge-Weber disease, is provided by Drs P. Huttenlocher and J. H. Tonsgard. The section on the management of Reye's syndrome is of particular interest since this life-threatening disease yields to intensive therapy with very gratifying results.

A chapter on transient ischemic attacks, with emphasis on the biochemistry of atherothromboembolism, the management of patients with TIA and a discussion of antiplatelet drugs, by C. Warlow, a discussion of the neurochemistry of aging and senile dementia by D. M. Bowen and A. N. Davidson, chapters on the latest findings in songiform virus encephalopathy (Creutzfeldt-Jakob disease) and the treatment of Bell's palsy, both written by W. B. Matthews, completes this 254-page book.

The book is well written, the topics are well chosen, the discussions are concise and to the point, and the references were well selected. All in all, this is a worthwhile, relatively inexpensive way to remain in touch with recent advances in the scientific basis of clinical neurology and some of the latest concepts and treatment modalities.

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RECENT ADVANCES IN ANAESTHESIA AND ANALGESIA—Number Fourteen—Edited by R. S. Atkinson, MB, BChir, and C. Langton Hewer, MB, BS, MRCP. Churchill Livingstone Inc., 1560 Broadway, New York, NY 10036, 1982. 182 pages, $29.00 (softbound).

This book, which reviews aspects of anesthesia practice, is the latest in a venerable series that began 50 years ago, when the first edition was one of the few sources of up-to-date anesthesia literature. There is no shortage of publications at present and the series now attempts to provide authoritative synopsis of current thought and in this it succeeds.

That the book is written by British practitioners is reflected by the fact that some of the chapters concern drugs not available in the United States, such as nonbarbiturate intravenous induction agents. Other topics are of interest to anesthesiologists irrespective of geographical location; for example, metabolism and toxicity of volatile anesthetic agents, anesthesia for ambulatory blood transfusion, relief of pain and chronic pain. The chapter on the preoperative assessment of cardiovascular disease is a model of good advice on this topic and the section on awareness during anesthesia deals with a topic barely covered in current anesthesia literature. There is an excellent discussion on the basis for and the clinical application of spinal narcotics which is refreshingly thoughtful and goes some way toward putting these techniques in their proper perspective.

The book is well presented, free of typographical errors and, for a multiauthored book, maintains an easily read and even style. For these reasons, it may be recommended to both anesthesiologists and residents. However, when cost is taken into account, the American Society of Anesthesiologists' refresher course book at approximately 20 percent of the price of *Recent Advances,* may be a better buy.

F. PETER BUCKLEY, MB, BS, FFARCS
Assistant Professor of Anesthesiology
University of Washington School of Medicine
Seattle

In Memoriam

California Medical Association

BYERS, WILLIAM M., Crescent City. Died April 12, 1982, aged 86. Graduate of the University of Illinois College of Medicine, Chicago, 1924. Licensed in California in 1924. Dr Byers was a retired member of the Los Angeles County Medical Association.

CAMERON, WILLA A., South Pasadena. Died April 12, 1982, aged 91. Graduate of the College of Physicians and Surgeons, Medical Department, University of Southern California, Los Angeles, 1917. Licensed in California in 1917. Dr Cameron was a retired member of the Los Angeles County Medical Association.

FRANKLIN, HAROLD J., Daly City. Died April 12, 1982, aged 69. Graduate of Howard University School of Medicine, Washington, DC, 1940. Licensed in California in 1943. Dr Franklin was a member of the San Francisco Medical Society.

GANS, EDWARD WOLF, Walnut Creek. Died April 8, 1982, aged 72. Graduate of Loyola University School of Medicine, Chicago, 1937. Licensed in California in 1947. Dr Gans was a retired member of the Alameda-Contra Costa Medical Association.

GONZALEZ, RODOLFO M., Gardena. Died May 5, 1982, aged 61. Graduate of the George Washington University School of Medicine, Washington, DC, 1946. Licensed in California in 1947. Dr Gonzalez was a member of the Los Angeles County Medical Association.

GOTANDA, WILFRED I., Stockton. Died August 19, 1982, in Kauai, Hawaii of carcinoma of the liver, aged 72. Graduate of the University of Arkansas School of Medicine, Little Rock, 1933. Licensed in California in 1936. Dr Gotanda was a retired member of the San Joaquin County Medical Society.

HAMPTON, WILLIAM W., San Diego. Died April 4, 1982, aged 63. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1949. Licensed in California in 1949. MD degree from California College of Medicine, 1962. Dr Hampton was a retired member of the San Diego County Medical Society.

HELMS, ROBERT W., Oxnard. Died June 6, 1982, aged 73. Graduate of the Ohio State University College of Medicine, Columbus, 1932. Licensed in California in 1945. Dr Helms was a retired member of the Los Angeles County Medical Association.

HUDSON, CHARLES B., Oakland. Died September 9, 1982, in Oakland, aged 72. Graduate of the University of Southern California School of Medicine, Los Angeles, 1939. Licensed in California in 1940. Dr Hudson was a retired member of the Alameda-Contra Costa Medical Association.

KRIKES, NICHOLAS P., San Bernardino. Died November 17, 1982, in San Diego of myocardial infarction, aged 58. Graduate of the University of Southern California School of Medicine, Los Angeles, 1954. Licensed in California in 1954. Dr Krikes was a past president of the California Medical Association and a member of the San Bernardino County Medical Society.

LANGSAM, MAURICE J., San Diego. Died July 17, 1982, in San Diego, aged 80. Graduate of Boston University School of Medicine, 1928. Licensed in California in 1971. Dr Langsam was a member of the San Diego County Medical Society.

MANTLE, VERNE M., Irvine. Died April 13, 1982, aged 78. Graduate of Rush Medical College, Chicago, 1929. Licensed in California in 1929. Dr Mantle was a retired member of the Los Angeles County Medical Association.

MAY, LUCILLE BROWN, Bakersfield. Died July 17, 1982, in Bakersfield of cancer, aged 84. Graduate of the University of California Medical School, Berkeley-San Francisco, 1924. Licensed in California in 1924. Dr May was an associate member of the Kern County Medical Society.

MCGAUGHEY, WILLIAM M., Oakland. Died June 24, 1982, aged 69. Graduate of Harvard Medical School, Boston, 1939. Licensed in California in 1945. Dr McGaughey was a member of the Alameda-Contra Costa Medical Association.

MCLOUD, KEITH, Chula Vista. Died June 24, 1982, in Chula Vista, aged 55. Graduate of Cornell University Medical College, New York, 1952. Licensed in California in 1960. Dr McLoud was a member of the San Diego County Medical Society.

MICHENER, ROBERT CHARLES, Sacramento. Died May 3, 1982, in Berkeley, aged 35. Graduate of the University of California, Davis, School of Medicine, 1972. Licensed in California in 1981. Dr Michener was a member of the Sacramento-El Dorado Medical Society.

MORAN, GLENN L., Redding. Died April 21, 1982, of myocardial infarction, aged 59. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1952. Licensed in California in 1954. Dr Moran was a member of the Shasta-Trinity County Medical Society.

OVERHOLT, KENNETH E., Sacramento. Died May 15, 1982, in Sacramento, aged 69. Graduate of McGill University Faculty of Medicine, Montreal, 1940. Licensed in California in 1940. Dr Overholt was a retired member of the Sacramento-El Dorado Medical Society.

PATRICK, JOHN E., Oroville. Died May 20, 1982, in Oroville of heart disease, aged 73. Graduate of the State University of Iowa College of Medicine, Iowa City, 1940. Licensed in California in 1946. Dr Patrick was a member of the Butte-Glenn Medical Society.

PAYNE, DONALD I., Alameda. Died April 29, 1982, aged 62. Graduate of the University of California Medical School, Berkeley-San Francisco, 1943. Licensed in California in 1944. Dr Payne was a retired member of the Alameda-Contra Costa Medical Association.

ROBERTSON, JAMES H., Arcadia. Died July 14, 1982, in Springfield, Missouri, aged 67. Graduate of Washington University School of Medicine, St. Louis, 1940. Licensed in California in 1941. Dr Robertson was a retired member of the Los Angeles County Medical Association.

ROSENZWEIG, MOISE, Los Angeles. Died July 21, 1982, aged 70. Graduate of Regia Università degli Studi di Pavia, Facoltà di Medicina e Chirurgia, 1936. Licensed in California in 1955. Dr Rosenzweig was a member of the Los Angeles County Medical Association.

SATNICK, SOLL R., Santa Monica. Died May 6, 1982, aged 65. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1942. Licensed in California in 1942. MD degree from California College of Medicine, 1962. Dr Satnick was a member of the Los Angeles County Medical Association.

SCHOLL, ALBERT J., Los Angeles. Died May 16, 1982, aged 91. Graduate of Harvard Medical School, Boston, 1917. Licensed in California in 1924. Dr Scholl was a retired member of the Los Angeles County Medical Association.

SELLARDS, HENRY GRADY, JR, Clearlake Highlands. Died July 27, 1982, aged 45. Graduate of the University of Tennessee College of Medicine, Memphis, 1963. Licensed in California in 1979. Dr. Sellards was a member of the Mendocino-Lake County Medical Society.

SMITH, WILLIAM P., Yucca Valley. Died June 24, 1982, aged 67. Graduate of the University of Oregon Medical School, Portland, 1944. Licensed in California in 1951. Dr Smith was a member of the San Bernardino County Medical Society.

THOMAS, BERT S., Sacramento. Died April 29, 1982, in Sacramento, aged 87. Graduate of the University of California Medical School, Berkeley-San Francisco, 1920. Licensed in California in 1920. Dr Thomas was a retired member of the Sacramento-El Dorado Medical Society.

URY, OSKAR, San Francisco. Died June 15, 1982, aged 94. Graduate of Universität Heidelberg Medizinische Fakultät, Baden, 1911. Licensed in California in 1940. Dr Ury was a member of the San Francisco Medical Society.

ZAHRY, N. JOHN, Bakersfield. Died August 28, 1982, in Santa Barbara of myocardial infarction, aged 72. Graduate of Indiana University School of Medicine, Bloomington-Indianapolis, 1932. Licensed in California in 1933. Dr Zahry was a member of the Kern County Medical Society.

Idaho Medical Association

DOUGLAS, WALLACE S., Lewiston. Died in October 1982, aged 81. Graduate of Northwestern University Medical School, Chicago, 1927. Licensed in Idaho in 1937. Dr Douglas was a retired member of the North Idaho District Medical Society.

New Mexico Medical Society

MERIDETH, HOWARD W., Albuquerque. Died October 18, 1982, aged 74. Graduate of Indiana University School of Medicine, Indianapolis, 1932. Licensed in New Mexico in 1949. Dr Merideth was a retired member of the Albuquerque & Bernalillo County Medical Association.

NOTH, PAUL H., Los Alamos. Died September 20, 1982, aged 75. Graduate of the University of Minnesota Medical School, Minneapolis, 1931. Licensed in New Mexico in 1950. Dr Noth was a retired member of the Los Alamos County Medical Society.

ROSEN, ALBERT M., Taos. Died October 12, 1982, aged 68. Graduate of the Chicago Medical School, Chicago, 1940. Licensed in New Mexico in 1940. Dr Rosen was a member of the Taos County Medical Society.

Utah State Medical Association

DIUMENTI, GEORGE S., Bountiful. Died September 8, 1982, in Bountiful, aged 67. Graduate of Louisiana State University School of Medicine, New Orleans, 1940. Licensed in Utah in 1942. Dr Diumenti was a member of the Salt Lake County Medical Society.

Wyoming Medical Society

BEANS, ROBERT B., Casper. Died July 9, 1982, of injuries received in plane crash in Billings, Montana, aged 69. Graduate of Columbia University, College of Physicians and Surgeons, New York, 1938. Licensed in Wyoming in 1966. Dr Beans was a member of the Natrona County Medical Society.

THORPE, VIRGIL L., Newcastle. Died October 2, 1982, in Newcastle, aged 65. Graduate of the University of Louisville School of Medicine, Louisville, 1944. Licensed in Wyoming in 1947. Dr Thorpe was a member of the Northeastern Counties Medical Society.

The Medical Consequences of Nuclear War

The Absurdities of Collective Extinction

The Symposium on the Medical Consequences of Nuclear War in this issue authoritatively describes what is known would be the results of a nuclear holocaust, whether large as in a nuclear war or relatively small as in a nuclear attack on a single city such as Portland. The data presented are from experience to date with atomic and nuclear explosions and near explosions and experience with human behavior in these and other kinds of major disasters, together with known facts concerning the stockpiling of more and more sophisticated nuclear weapons here and abroad. The facts and the experience are real, and no doubt are accurate predictors of the effects of nuclear war. And, as is pointed out, if all the existing weaponry is used at one time, the actual extinction of the human race and many other kinds of life seems possible. But in virtually any use of nuclear weaponry modern medicine will be powerless to deal with the human havoc that will occur whether the attack be large or small, or wherever in the world it might occur.

In her article in this series Judith Eve Lipton uses the phrase "the absurdity of collective extinction." Webster* defines absurdity as "the quality of being inconsistent with obvious truth, reason or sound judgment, and therefore laughable or ridiculous." The papers in the Symposium describe much that is inconsistent with obvious truth, reason or sound judgment but what is described is far from being laughable or ridiculous. Rather the data and experience to date are terribly scary given the mind-sets and beliefs that hold sway at the present time here and elsewhere in the world. At first sight the idea of collective extinction may seem absurd in the full sense of Webster's definition. But something like it does occur among animals, as when whales apparently senselessly beach themselves and die, or even among humans, as in the senseless mass suicide of a religious cult in Guyana several years ago. Our understanding of mass psychology and the prevention or treatment of mass hysteria leaves much to be desired. In the context of avoiding a possible nuclear war this lack of knowledge and understanding is particularly serious.

Nuclear arsenals exist. It would be better if they did not, but they are with us and will be for some time to come. Many nations have nuclear weapons or the capability of producing them. There is no monopoly on the capacity to deliver nuclear warheads anywhere in the world. So it is the use of nuclear weapons that must be prevented if possible. This may not be easy, humankind being what it is. The medical profession is beginning to do its part by increasing the public awareness of the medical consequences of nuclear war and this should continue and become a worldwide effort of physicians everywhere. But more is necessary. Just as human behavior and life-styles are important in the prevention of many kinds of personal injuries and illnesses, so are human behavior and life-styles important in preventing the massive injuries and illnesses that will result from the use of nuclear weapons. Physicians the world over must now begin to concern themselves more specifically with the relationships of human nature and human behavior, in sickness and in health, to the prevention of nuclear war and the absurdities of collective extinction by these means.

—MSMW

*Webster's New Twentieth Century Dictionary Unabridged, 2nd ed. New York, Simon and Shuster, 1979, p 8.

The Medical Consequences of Nuclear War

Introduction

In introducing the four papers that address the issue of nuclear war and its medical consequences, there are two statements I feel provide a perspective for the reader. The first is the summary of a position taken by the American College of Physicians during their annual meeting in the spring of 1982:

The American College of Physicians believes there can be no adequate medical preparedness for the devastating medical consequences of nuclear war; prevention is the only reasonable medical response to the hazards posed by nuclear weapons. To foster prevention of nuclear war, the American College of Physicians endorses increased professional and public education about the medical consequences of nuclear war.[1]

The second statement is that of John W. R. Taylor, who for the past 22 years has been the editor of Jane's annual *All the World's Aircraft:* "Neither a growing acceptance by military leaders of the feasibility of limited nuclear warfare, nor a drift by the civilian population towards anarchy, via protest, offers a path to survival."[2] When two such diverse sources identify nuclear holocaust and its mediators, nuclear weapons, as beyond planned survival, then the medical profession must educate itself and be prepared to develop a strategy.

One approach to the issue is to develop a response to the question, can medicine cope with current nuclear technology? The articles included in this special section of the journal will provide a basis for formulating an answer. The medical profession has prided itself on the use of the scientific method when faced with the task of decision making. The ethical problems that are raised by rapidly expanding technology are not new, though for nuclear war come in a proportion that heretofore we have not addressed. However, examples abound of the ethical problems that new technology has forced on us. For example, as life-support systems have become more sophisticated, the definition of death, both medically and ethically, has become both complex and more confusing. Whereas the focus was on patients with acute irreversible injuries, it was expanded to include patients surviving because of a sophisticated technology such as chronic renal dialysis. With education, experience and debate, a philosophy is emerging that allows humane laws to be developed protecting both patients and physicians. In a similar vein, with the stakes being the survival of humankind as we know it today, all physicians must become convinced that prevention of a nuclear war is the only alternative worthy of our pursuit.

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REFERENCES

1. American College of Physicians: The Medical Consequences of Radiation Accidents and Nuclear War (Position Paper). Philadelphia, April 16, 1982

2. Taylor JWR (Ed): All the World's Aircraft, 1981-1982. London, Jane's Publishing, 1982

Nuclear Weapons and Civil Defense

The Influence of the Medical Profession in 1955 and 1983

HOWARD KORNFELD, MD, *San Francisco*

In the September 1981 issue, Malcolm Watts, the editor of this journal, stated that

> There is a growing sentiment among many physicians that somehow the medical profession should do something to bring some sanity into the worldwide approach to the proliferation of nuclear armaments . . . An effective course of action by the profession, as physician to the world so to speak, is sorely needed, but is not yet identified.[1(p234)]

Medical professionals who seek an effective course of action will benefit from a knowledge of history. In this case, there are two parallel and intertwined histories. One concerns the development of nuclear weapons by the government; the other, the medical community's response to these military and political events.

This article will begin by focusing on a segment of this history, the events surrounding the publication in October 1955 of a special issue of *California Medicine* (then the name of the official journal of the California Medical Association [CMA] and subsequently renamed and expanded into THE WESTERN JOURNAL OF MEDICINE). The entire issue was devoted to civil defense in nuclear warfare. An evaluation of these writings reveals a failure by the authors to adequately differentiate between the nuclear war disasters that they were addressing and the conventional war situations with which they were familiar. The tendency to think of nuclear war in prenuclear terms had an impact, not only on public health planning, but on military planning as well.

These historical events in some ways resemble the situation today, and they have important implications for the role of the medical profession in the development of public policy. In 1983, as in 1955, there are unique opportunities to halt the nuclear arms race. The medical community today, however, with its greater insight and knowledge, is in a better position to help reverse this dangerous process.

The Perception of the Medical Community in 1955

There were nine articles in the special 1955 issue of *California Medicine*.[2-10] They dealt with a wide range of topics, including plans for a civil defense medical organization in California, the medical aspects of atomic and thermonuclear warfare, the emergency treatment of burns in mass casualties, the management of hysteria in catastrophes and the procurement of blood and plasma in major disasters. An editorial entitled "Civil Defense—Your Responsibility"[11] followed the articles, as did a report of the CMA Woman's Auxiliary entitled "The Part Played by Your Auxiliary in Civil Defense."[12]

Our medical colleagues in the mid-1950s faced a rapidly evolving technologic and military environment in their efforts to make judgments about matters of civilian defense and medical disaster planning for nuclear war.

They found some comfort in the example of previous military experiences, though these were peculiarly out of date by 1955. In an apparent reference to the bombing of Pearl Harbor, the issue's editorial states that "Our nation cannot afford again to be unprepared if and when the enemy strikes. . . . think back only a little more than a decade, when proud ships of our navy were sunk at anchor."[11(p314)]

The editorial goes on to remind us that American physicians had traditionally played an active role in the nation's defense:

> In fact, seldom in the annals of history has a profession rallied as did ours during World War II when one-third of the total strength of our profession volunteered and served with the armed forces. Again our nation faces a real crisis.[11(p314)]

The rationale for civil defense against atomic weapons was found in the prenuclear era:

> As to the necessity for having a civil defense organization, one merely needs to refer to the lessons gained by the Germans, English, Japanese and other nations during World War II.[2(p259)]

The discontinuity of the nuclear present of 1955 from the conventional past was recognized, at least in one respect. American civilians for the first time were seen to be vulnerable to enemy attack. The issue's lead article states the following:

> In past wars, the enemy has never seriously struck at our shores or our cities. In future wars the enemy will be successful, in varying degrees, in bombing our cities and industries just as we will be in destroying his cities and population centers. Civilians will no longer be . . . protected. . . . There will be no front lines.[2(p259)]

They responded to this new circumstance with a determination to apply their medical knowledge to insure national survival and predominance in a nuclear conflict. Another article[3] opens with the following statement:

> If and when the nations of the world come to armed conflict

Refer to: Kornfeld H: Nuclear weapons and civil defense—The influence of the medical profession in 1955 and 1983 (Medical Consequences of Nuclear War Symposium). West J Med 1983 Feb; 138:207-212.

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to determine which of the two great economic and political structures shall prevail, it is certain that our cities will be attacked in such ways that enormous numbers of casualties will instantly make the greatest medical task in all history.[p268]

Their strategy was to intensify existing concepts of disaster medical management. For example, the greatest problem in civil defense was thought to be the treatment of mass casualties:

In all the United States wars from the Revolutionary through World War II there was a total of 1,160,552 casualties that survived wounds. Civil Defense is currently planning to take care of 5,000,000.[10(p311)]

If 70 critical target areas were attacked simultaneously, a scenario for which the authors wished to be prepared, "there would be 13.5 million living and dead [casualties] immediately afterward, 8.2 million living casualties after the first day."[2(p260)]

Another essay[3] suggested the scope of injuries to be expected and the great responsibility that physicians would have in these matters:

In some phase of the effort, physicians will be required to treat practically every condition to which the human body can be subjected. . . . Regardless of the type of practice now followed, physicians are all trained in the basic fundamentals of medicine and surgery, and must be prepared upon a moment's notice to make themselves fit into the effort wherever they are needed. . . . During disaster, the first responsibility is to the casualties. This implies that the physicians will stand fast and resist the natural impulse to flee. It also means that the normal anxieties about family, friends and possessions must be quickly overcome and that all will report for duty promptly.[3(pp268-269)]

It was suggested that 6,000 "improvised hospital (MASH [mobile army surgical hospital]) units"[2] would be required nationwide and that these would be supplied by 20 major medical warehouses. Already, 20 MASH units had been ordered for California.

The importance of regimentation in training for civil defense is emphasized, as is the need for overcoming fear:

Over and over in combat one sees the soldier, even in a borderline panic state, repeat successfully functions learned in basic training. Here is the true reason for the repetitive, almost *ad nauseam,* drill of soldier, policeman, fireman or civil defense worker. . . . What counts is repetitive practice . . . without conscious thought, since anyone may well lack capacity for conscious action as fear paralyzes his cortex.[7(p298)]

Fear in the citizenry could be prevented by another technique. In explaining the risks of this type of warfare in civil defense training, it was suggested (as quoted in *Civil Defense News,* Utica, NY, vol 1, No. 3, February 1, 1951) to

Explain to every citizen that even though A-bombs do fall in a given area his chances of survival are good. Instead of saying that two atomic bombs might cause "80,000 casualties" in a metropolitan area like Los Angeles, say rather that casualties would be "not more than two out of every 100 persons in Los Angeles county."[7(p298)]

The authors were aware of the larger destructive capability of the new thermonuclear weapons,[4] but they did not conclude that their casualty figures, based on the smaller atomic bombs, were obsolete. In addition, certain known and important features of nuclear weapons were ignored. The initial US test of the hydrogen bomb in 1954, code named "Bravo," had revealed that lethal fallout could spread much farther than was previously suspected.[13] A Japanese fishing boat was unexpectedly irradiated with fallout near the detonation in the South Pacific. Although the geographic extent of fallout is noted in one of the articles, the intensity of the dose is not included, thus failing to convey to readers the true scope of the danger. Another serious omission is the failure to describe the possibilities for fire storms, which occurred at Hiroshima and had occurred in Dresden and Hamburg[14] during World War II. A mass fire such as a fire storm could increase the lethality of a nuclear detonation by a factor of five.[15]

Both evacuation and sheltering of the population were mentioned in the civil defense articles in *California Medicine,* but no details were provided. Stein and coworkers noted the following:

Studies are being made with regard to dispersal and evacuation of the population. Since thermonuclear weapons are fully capable of destroying large cities, the only real protection against these weapons is either not to be there at the time of the blast or to have as much protective shelter as possible.

The only real defense against the thermonuclear weapons is dispersal of the population if there is sufficient warning time—three or more hours.[2(p267)]

How the large metropolitan areas were to be evacuated in the few hours available was not specified.

The picture that emerges from an evaluation of these writings is of a medical community that was attempting to acclimate itself to the new and terrible possibilities of nuclear war and to integrate itself within the overall military strategy of the time. Physicians tended to think of nuclear weapons in terms of the prenuclear military experience with which they were familiar. The response to the new vulnerability was to build on previous ideas of medical aid and trauma care. There was no evidence available to show that the medical system could handle the 13.5 million expected casualties. Furthermore, this figure is unrealistically low; conservative estimates of the destructiveness of the 1955 Soviet arsenal indicate that 40 million casualties could have been expected (see below). More important, the authors showed little or no insight that their estimates would soon be obsolete by at least an order of magnitude as a result of the introduction of hydrogen bombs and ballistic missiles.

Concepts of evacuation and sheltering of the population were mentioned, but not evaluated for efficacy or feasibility. Certain known and important effects of the weapons were not described. Physicians were to render care and—in a romanticized, superhuman pose—to reassure a traumatized and panic-stricken population. Regimentation was to be used to prepare for this situation and subtle deception was in order to prevent fear during civil defense training.

Not once in the entire issue was the subject of the physician's role in the prevention of nuclear war mentioned.

The Nuclear Arms Race in 1955

The state of nuclear armaments in 1955 was far less advanced than it is today. Nevertheless, two of the

three primary technological innovations of the postwar period were already taking place. The first two, atomic and hydrogen bombs, awaited the third, intercontinental ballistic missiles (ICBM's), which were not to be introduced for several more years.

The Soviet Union first detonated an atomic bomb in August 1949, a little more than four years after the United States did. It used the same basic process, nuclear fission,[16] and the same fuel, plutonium,[17] that the United States used in both the first atomic test at Alamogordo, New Mexico, and in the destruction of Nagasaki on August 9, 1945. The Hiroshima bomb, exploded three days earlier, had utilized enriched uranium as its fuel—the other technique known at the time for achieving nuclear fission.[18] It is estimated that these weapons released an energy of between 12.5 and 22 thousand tons (12.5 to 22 kilotons) of TNT (trinitrotoluene).[18]

The United States began testing thermonuclear components in its atomic bombs in 1951. They utilized isotopes of hydrogen in the process of nuclear fusion and a successful detonation of a cumbersome device took place in 1952. Its destructive energy exceeded the first atomic bombs by a thousandfold. Because the first atomic test had exceeded by a thousandfold the energy released by the largest conventional bombs of World War II, the hydrogen bomb represented a millionfold increase in destructive force. This had been achieved in less than a dozen years of scientific research on nuclear explosives. By 1954 the United States had a compact hydrogen bomb, deliverable from an aircraft and equivalent to 15 million tons (15 megatons) of TNT.[19]

The Soviet Union followed suit with a thermonuclear experiment in 1953 and a full-fledged deliverable hydrogen bomb of several megatons by November 1955, about a month after the publication of the *California Medicine* civil defense issue.

The United States nuclear arsenal in 1955 has been estimated at about 2,000 warheads.[20] The Soviet Union's stockpile of fissionable material at this time has been estimated at 30 percent of the US supply,[21(p174)] indicating their capability to produce about 600 atomic bombs of similar design. To conservatively estimate the destructiveness of the 1955 Soviet arsenal, it is assumed their warheads averaged 20 kilotons, the size of the first atomic bombs. If this explosive quantity is converted to a standard unit, termed *equivalent megatons,*[22] and using a method developed by former Defense Secretary Robert McNamara,[23(p86)] the consequences of a successfully targeted Soviet attack can be estimated at 40 million deaths and serious injuries.

These weapons could only be delivered by manned aircraft in 1955, but research on ballistic missiles was well under way and the future threat of enemy missiles was officially publicized.[21(p367)] At that time 10 to 12 hours of flight time were needed by the bombers for intercontinental travel. They were capable of speeds of up to 600 mph (966 km per hour).[21(p66)] The ballistic missile, to be deployed on land and on submarines in the next few years,[21(p163)] would attain speeds of 15,000 to 20,000 mph (24,000 to 32,000 km per hour)[23(p15)] and traverse intercontinental distances in less than 30 minutes.

Although air defenses were constructed during this period, including the Distant Early Warning (DEW) system in the arctic circle, they were considered only partially effective against manned aircraft.[21(p163)] They were obsolete by 1957 and 1958 when both the United States and the Soviet Union placed satellites in orbit and successfully tested intercontinental ballistic missiles.[21(pp360-375)]

With the quantitative growth and the qualitative changes in nuclear weapons came a new perspective on their use and deployment. In 1953 a report to Congress on nuclear weapons by the Chairman of the United States Atomic Energy Commission included the following:

> No longer are they looked upon only as devices to be used in a "Hiroshima-type" way against cities and industrial areas. It is now possible to have a complete "family" of atomic weapons, for use not only by strategic bombers, but also by ground support aircraft, armies and navies. The Department of Defense is very much aware of this change in concept, and atomic weapons are being incorporated into the operational plans for all three of the armed services. This, quite naturally, has greatly increased the demand for atomic weapons—to an entirely different order of magnitude than obtained a few years ago.[21(p128)]

By 1955 the United States had deployed nuclear depth charges for use at sea and nuclear shells for guns, artillery and antiaircraft missiles. They were as small, according to *The New York Times,* as 5 in (12.7 cm) in diameter.[21(p128)] These new armaments were eventually characterized as "tactical nuclear weapons." Secretary of State John Foster Dulles stated in early 1955 that "small tactical atomic weapons probably would be used if the United States became involved in any major military action anywhere."[21(pp139-140)]

This governmental policy and the public willingness to be the first to use nuclear weapons in conventional wars around the world have persisted to the present.

The doctrine of limited nuclear war that was developed during this period was examined by an analyst writing for the *Bulletin of the Atomic Scientists* (May 1956, p 157, quoted by Noel-Baker):

> NATO's [the North Atlantic Treaty Organization's] basic strategy . . . is based upon a nuclear concept; we will use, it is said, tactical A-weapons. . . . In a thickly settled area like Western Europe this is a . . . self-defeating strategy, for no such . . . nuclear war could be limited . . . it is virtually impossible . . . to distinguish clearly betweeen military and non-military targets. . . . A nuclear war in Western Europe would almost certainly spread in a "no-holds-barred" conflict, and Western Europe . . . would emerge a desert.[21(pp146-147)]

Philip Noel-Baker, who was awarded the Nobel Peace Prize in 1959, commented that

> This was a most terrible development in the preparation for war. The United States example was quickly followed by Russia and Britain. The tactical weapons were designed and manufactured with amazing speed.[21(p128)]

Disarmament Negotiations in 1955

The year 1955 resembled the present in the opportunity that existed for a negotiated end to the nuclear arms race.

US policies toward the control of nuclear weapons began in the early postwar period with the Acheson-Lilienthal Report and the Baruch Plan—which was presented to the United Nations Atomic Energy Commission in 1946. Because of the unwillingness of either the United States or the Soviet Union to compromise on key aspects of the agreement, primarily related to the timing of certain provisions, little progress was made.[24] After several more unproductive years, the British and the French achieved a breakthrough when they introduced a "carefully wrought plan for disarmament," which was also endorsed by the United States. On May 10, 1955, the Soviet Union accepted key provisions of this proposal. Further negotiations on this document may have yielded a broad agreement. Unfortunately, our government took another direction. Glen T. Seaborg, who was Chairman of the US Atomic Energy Commission from 1961 until 1971, describes the course of events: "The rejoicing was premature. . . . serious doubts had arisen in the US government about some of the disarmament positions that our representatives had previously espoused or endorsed."[24] According to Dr Seaborg, both the Atomic Energy Commission and the Department of Defense questioned whether nuclear disarmament of any kind accorded with the security interests of the United States. The objections had not been emphasized earlier because, in his opinion, those holding them had not taken the ongoing disarmament negotiations seriously.

His description continues as follows:

> The near agreement in 1955 changed all that. Under the pressure of the dissent within his administration President Eisenhower ordered "a broad reappraisal of disarmament policy," and in September 1955 Harold Stassen, who had been appointed by the President to the new position of special assistant for disarmament, was forced amid great embarrassment to "place a reservation on"—in effect, to repudiate—all previous US disarmament positions.[24]

Two Distinct Frames of Reference

A perspective on nuclear weapons is provided by Solly Zuckerman,[25] who served as the chief scientific advisor to the Prime Minister of Great Britain from 1960 to 1966. As Lord Zuckerman writes in the preface of his recent book *Nuclear Illusion and Reality,*

> What is clear when one looks closely is that discussions of nuclear weapons fall into two distinct and logically disconnected frames of reference. The first embraces the doctrine that "atom and hydrogen bombs" could be used to advantage in certain operations of war. The second defines the concept of deterrence. By this is meant that no sane government would embark upon military action leading to the use of nuclear weapons if this entailed the risk that it could be annihilated by a nuclear onslaught delivered by its enemy.(p x)

The first frame of reference views nuclear weapons as tools for the extension of conventional warfare. The second frame of reference, the concept of deterrence, recognizes the immense destructive power in these weapons and thus

> provides no justification for either side to increase the size of its nuclear arsenal above the minimum level that would deter. There is, in fact, no realistic and no theoretical justification for the belief that nuclear weapons could ever be used as a rational extension of conventional armaments.[25](p x)

By 1955 it appears that military planners had chosen the first of Zuckerman's "frames of reference," the one for which there was no "realistic or theoretical justification." Rather than being a deterrent to prevent war, the new weapons were seen to have many uses in the conduct of war.

Examples of this choice were the decision to develop large numbers of atomic bombs—a strategy more appropriate for the weapons of the prenuclear era—and the decision to deploy these weapons as if they were conventional arms, on the sea and on the battlefield. The weapons were targeted on the adversary's military forces as well as his cities. The willingness to use nuclear weapons first was emphasized.

The decision in the early 1950s to develop the hydrogen bomb, against the advice of the most prominent scientists at the Atomic Energy Commission,[19] was also an attempt to gain "advantage" from nuclear arsenals. Enrico Fermi and Isador Rabi, two members of the commission's General Advisory Committee, considered the project "evil."[19] This "superbomb," as it was called, which could kill millions of people in one detonation,[26(pp13-48)] made legitimate the tendency to think of the atomic bombs as small or "tactical," even though two atomic bombs killed almost 200,000 Japanese civilians in 1945 and brought a major world war to a swift conclusion.

Into which frame of reference did the authors of the special *California Medicine* issue place the use of nuclear weapons and what influence did this have on the critical public discussions of that era? This analysis of their thinking has shown that they regarded the threat of nuclear war in a manner better suited to the military threats of an earlier time. It is likely that the attitude of the medical profession in 1955 contributed to an overall acceptance by the people of the United States of nuclear warfare as a rational extension of conventional conflict. If so, they contributed as a group to a climate more conducive to an expansion of nuclear arsenals than to serious disarmament negotiations.

Today's Nuclear Arsenals

It has been 27 years since the publication of these writings on civil defense. In the interim, many unsuccessful attempts have been made to halt the growth of nuclear arsenals and many innovations in the weapons of mass destruction have been introduced. Today we find ourselves in a new and dangerous phase of the nuclear arms race.

Contemporary arsenals are much larger than those of 1955. The Secretary-General of the United Nations estimated in 1980 that the United States possessed between 25,000 and 33,000 nuclear warheads, with between 4,000 and 8,000 megatons of destructive force.[27] The estimate for the Soviet Union was between 11,000 and 15,000 warheads and between 7,000 and 11,000 megatons of destructive force. The habit of deploying these weapons as if they were conventional armaments continues. For example, the United States is reported to have 7,000 tactical nuclear weapons in Europe,

1,700 in the Far East and 2,500 aboard naval vessels at sea.[23(pp211-222)] The Soviet Union is also reported to have large numbers of tactical nuclear weapons. Today's equivalent megatonnage exceeds that of 1955 by at least a hundredfold. Moreover, the capability of manufacturing nuclear weapons has spread far beyond the borders of the present nuclear powers. At least ten additional nations could manufacture nuclear weapons in the next decade, if they chose to do so.[28] In addition, today's more sophisticated, computer-dependent weapons sit on highly accurate missiles that threaten the stability of the opponent's deterrent force. The growing possibilities for accidental or unauthorized nuclear war[29] further intensify the current risk.

Recent Attitudes in Medicine and Science

The effects of nuclear war from contemporary arsenals are proportionally greater than they were in 1955. A large attack by the Soviet Union on military and economic targets in the United States would produce prompt fatalities on the order of 100 million.[26(pp63-108)] This figure only begins to estimate the actual devastation because, as reported by the Congressional Office of Technology Assessment, "The effects of a nuclear war that cannot be calculated are at least as important as those for which calculations are attempted."[26(p31)] The ensuing breakdown of society, including mass starvation[31] and infectious epidemics,[32] would further increase the death and disease. Moreover, the possibility of an ecologic catastrophe cannot be eliminated.[26(pp109-118)]

The medical and scientific communities have made statements in the recent past that have recognized the overwhelming nature of a nuclear attack. In 1981 the American Medical Association (AMA) issued a statement as follows:

> It is in a spirit of concern that the AMA Board of Trustees believes that it is incumbent upon the Association to inform the President and the Congress of the United States of the medical consequences of nuclear war and that no adequate medical response is possible.[33]

The American College of Physicians confirmed the AMA's findings and in 1982 issued a "position paper" that stated in part:

> The American College of Physicians believes that there can be no adequate medical preparedness for the devastating medical consequences of nuclear war; prevention is the only reasonable medical response to the hazards posed by nuclear weapons.[34]

In a near-unanimous statement, the members of the National Academy of Sciences in 1982 acknowledged that "science offers no prospect of effective defense against nuclear war and mutual destruction."[35] They called upon the President and the Congress "to avoid military doctrines that treat nuclear explosives as ordinary weapons of war."

Current Implications

Civil defense programs have passed through several stages since 1955. A detailed analysis of the intervening and current programs will not be attempted here. It is accurate to say, however, that the threatened destruction, unmanageable in 1955, has grown immeasurably.

During the late 1950s and early 1960s, government agencies promoted the construction of fallout shelters. Some have called what ensued "a shelter psychosis,"[22] with persons building and preparing to defend with munitions their own private underground shelters. In more recent years, in the midst of the current nuclear arms buildup, the Federal Emergency Management Agency (FEMA) has perceived an inadequacy in US civil defense capabilities and has proposed a multibillion dollar program designed to relocate the population, over a period of several days, in an international crisis. They believe that the plan will allow for the survival of 80 percent of the population of the United States in an all-out nuclear war. The plan calls for the evacuation, at the President's order, of several hundred urban areas to "host" communities.[36] On arrival, the 145 million evacuees are to dig underground shelters or to otherwise find protection from the lethal fallout that can be expected to blanket the nation for days, if not weeks.[37,38]

As a rationale for this Crisis Relocation Plan (CRP), civil defense advocates cite a similar Soviet evacuation program. Realistic analysis, however, of the Soviet plan shows it to consist primarily of neglected instruction manuals, shelter signs and an apathetic bureaucracy.[39-41] The Central Intelligence Agency summarized a study it conducted in 1978 of the Soviet civil defense program as follows:

> They cannot have confidence . . . in the degree of protection their civil defense would afford them. . . . We do not believe that the Soviets' present civil defenses would embolden them deliberately to expose the USSR to a higher risk of nuclear attack.[42]

FEMA's Crisis Relocation Plan, in the opinion of the editors of *The New York Times,* is based on "hallucinations about Soviet civil defense" (April 3, 1982, p 18).

Dozens of local communities have rejected the FEMA crisis relocation strategy (*San Francisco Chronicle,* June 28, 1982, p 8). They cite numerous reasons why they believe the plan is not only infeasible, but dangerous. Their objections range from the logistic problems of transporting millions of panic-stricken people into rural areas, to the question of feeding and sheltering these people during the process, to the unmanageable task of providing extensive fallout protection in the host areas, to the futility of the whole project in an era when missiles can be retargeted in a short period of time.[43,44] Most alarming to those who have studied the plan is its capacity to heighten international tensions and, if carried out, actually precipitate a nuclear war.

Mr T. K. Jones, the Deputy Undersecretary of Defense for Strategic and Nuclear Forces, has underscored the seriousness with which the federal government regards these ideas when he recently advocated publicly ("US Will Revive Civil Defense," *The Los Angeles Times,* January 15, 1982, p 1) that American citizens could build primitive dugout shelters for protection

from nuclear attack: "Everybody's going to make it . . . if there are enough shovels to go around. . . . Dig a hole, cover it with a couple of doors and then throw three feet of dirt on top. It's the dirt that does it."

Perhaps the most significant feature of civil defense programs for all-out nuclear war is the prominent role they play in the plans of those who advocate strategies of victory in nuclear war.[45,46] For example, the implications of our allegedly inadequate civil defenses were cited by one analyst of the "war-fighting" school, when he made the following observation in a prominent political science journal: "As long as American society is essentially unprotected by . . . civil defense, the US will have to lose any process of . . . escalation against the Soviet force posture."[45] The only way to avoid defeat, and to "dominate" the "escalation," according to this writer, is to significantly expand both military and civilian defense capabilities. What he hopes for is best expressed in the title of his article, "Nuclear Strategy: The Case for a Theory of Victory."

The American Medical Association has recently decided to evaluate the federal crisis relocation plan.[47] Their deliberations on this complex issue, if thoughtful, can strengthen the force of reason. An inadequate examination, or a casual endorsement, could dilute the notable contribution already made by the association and deepen the process of delusion.

Conclusions

The opportunity exists today, as it did in 1955, to halt the nuclear arms race, to freeze the further development of nuclear weapons and their delivery systems and to begin the process of bilateral disarmament that is essential to the survival of our nation. The voices that describe the mirage of survivability in nuclear holocaust are often the same voices that argue for more numerous and usable nuclear weapons. The informed participation of physicians is essential in dissuading those who would believe that winning a nuclear war is possible.

Preventive medicine today requires that we understand the history of a previous era, when the medical profession uncritically endorsed a civil defense plan for all-out nuclear war. At a crucial time in history, when the nuclear buildup could have been curtailed, our colleagues failed to provide the scientific and health policy perspectives that were needed.

Today the arsenals are larger and the margin of error slimmer. Not every physician can become intimately involved in the complexities of arms control and nuclear weapons policy. But all of us can join the AMA in making a clear statement to our government and our people: that the medical consequences of nuclear war are awesome and without precedent; that adequate preparation or meaningful response to a nuclear holocaust is impossible, and that prevention is the only key to our survival.

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An Epistemology of Nuclear Weapons Effects

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Nuclear war has been called unthinkable, and thus we may have suspected it is also unknowable. If it cannot be known, then it can be more easily dismissed from conscious concern. It may haunt our dreams and our art. It may exert a powerful pervasive influence on the values and psychology of our culture. But, believing it is unknowable, we have remained ignorant while its threat has grown year by year and day by day. So it is important that we learn something about nuclear weapons and nuclear war, and that we challenge that ignorance.

In fact, much is known about the effects of nuclear weapons. The "experiments," if we may use that word, of Hiroshima and Nagasaki contributed a great deal of information about the atomic bomb, its medical consequences and its social and human significance. In Hiroshima, a lively city of 300,000 people was turned into a desolate radioactive desert by a single 13-kiloton bomb,[1] which is relatively small by today's standards.

While we use these historical events to help us understand the effects of nuclear weapons, it is essential to remember that any use of thermonuclear weapons today will be different in several important ways. One difference is that the Hiroshima and Nagasaki bombs were fission devices with a destructive force comparable to 13,000 to 18,000 tons of TNT (trinitrotoluene). Within a few years after the war, fusion bombs—what we know as hydrogen or thermonuclear bombs—had made the atomic bomb obsolete. The hydrogen bombs, which make up most of today's arsenals, are orders of magnitude more powerful and more destructive than the atomic bombs. The world's arsenals today contain about 50,000 nuclear warheads.[2] Most strategic warheads are of greater destructive power than the Hiroshima bomb, many of them in the megaton range. A megaton is comparable to a million tons of TNT, which has been described as enough explosive to fill a freight train 200 miles long. World War II lasted for six years and claimed 50 million lives. The combined firepower exploded during that war, including the two atomic bombs dropped on Japan, equaled 3 million tons of TNT, or 3 megatons. Many of today's weapons have destructive yields as great as 10 or 20 megatons, many times the entire firepower of World War II. This is a quantitative difference so large as to be in fact a qualitative difference. These are not weapons of war, but weapons of a form of annihilation that is almost impossible to comprehend.

Even if it cannot be comprehended, annihilation of this sort can be computed. Scientific analyses of nuclear weapons and their explosions have produced a copious literature, complete with graphs, formulae and even small plastic bomb effects slide rules that predict the effects for any given set of conditions (Figure 1). There are carefully developed models from which projections can be made. In fact, the US Arms Control and Disarmament Agency has worked out the likely effects of nuclear weapons targeted at every city in the country with a population of 50,000 or more. Some smaller towns are also included depending on their strategic significance. Calculations can be adjusted for whether a device is exploded in the air, which maximizes blast effects, or on the ground, which maximizes radioactive fallout. Physical characteristics have been calculated for every possibility of yield, height of explosion, time of day, weather conditions, terrain or kinds of city buildings to be bombed.

Nuclear weapons produce many kinds of destructive effects, which fall into three main categories: heat, or thermal radiation; blast and ionizing radiation, and immediate and long-term effects. At the moment of the explosion, when the energy inherent in the binding forces between the subatomic particles in atoms of plutonium, deuterium and tritium is released in an almost instantaneous chain reaction, the bomb parts themselves are instantly gasified at a temperature in the range of 10 million degrees centigrade or more, comparable to the center of the sun. Immediately radiation, primarily in the form of gamma rays, is released as a flash of intense bluish white light visible for hundreds of miles. The fireball then begins to form, still fractions of a second from the time of the explosion, and the air absorbed by it radiates a thermal pulse—a wave of blinding light and intense heat—which is a third of the energy and destructive force of a nuclear weapon. When the fireball touches the ground, it vaporizes or incinerates everything within it. The thermal pulse lasts for about ten seconds and can cause second-degree burns to exposed human beings miles away.

Also at the moment of the explosion, pressure within

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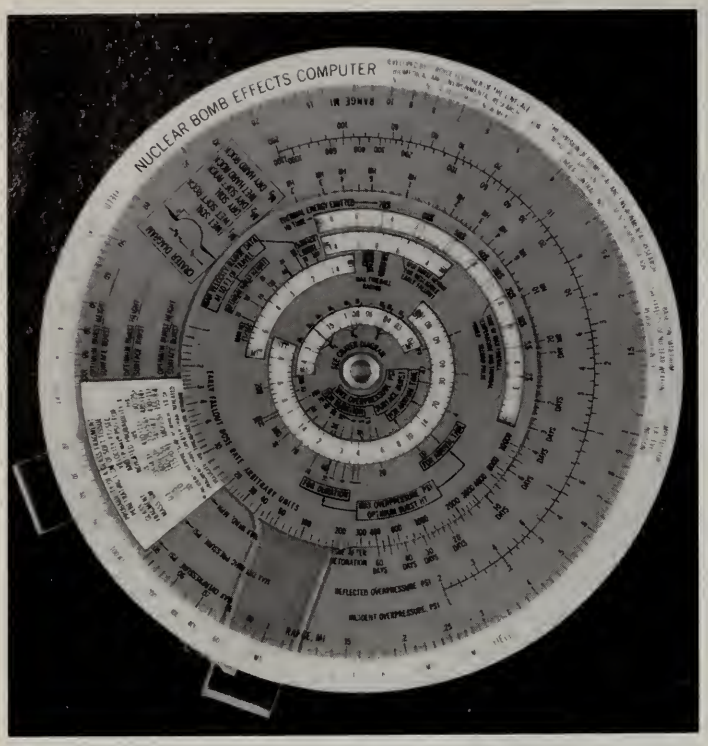


Figure 1.—The Nuclear Bomb Effects Computer, developed by the Lovelace Biomedical and Environmental Research Institute, Inc., Albuquerque (from Glasstone S, Dolan PT[8]).

the gaseous space is millions of times atmospheric pressure. A fusion bomb essentially duplicates the mechanism by which the sun's radiant energy is produced. It is confined initially into a very small space and generates enormous explosive pressure. As the fireball expands (to a mile in diameter for 1 megaton) this pressure is transmitted to far beyond the limits of the fireball in a blast wave, which is the major immediate destructive force of a nuclear weapon.

What, then, do we know about the effects of these phenomena on human beings? To answer this question, let us consider the example of a one-megaton airburst over Portland's Burnside Bridge. It is of course unlikely that a single nuclear weapon would be targeted at Portland—much more likely that there would be several,[3] perhaps staggered over the course of a day. Still, one must pick an arbitrary set of conditions to make the necessary calculations. This is a somewhat conservative, therefore useful, model to understand the medical realities of the use of nuclear weapons.

A Model of a Nuclear Attack

Imagine that at a specific time, perhaps during a period of increasing tension between the United States and the Soviet Union, perhaps during debates about the advisability of first-strike tactics, Portland is hit by a 1-megaton explosion eight times the destructive power of the Hiroshima bomb.*

It would produce within microseconds a dazzling white light, continuing for as long as 30 seconds. Simultaneously, a searing, silent heat flash would melt windows, cars, lamp posts and everything else within a radius of 3 miles (4.8 km), igniting everything flammable miles beyond. Within a radius of 1½ miles (2.4 km) people would be instantly vaporized or burnt into charred black corpses. Within this circle, everything would be utterly destroyed and all people would be killed.

Much like thunder follows lightning, a few seconds after the flash the blast wave would hit. Because it travels at a speed just slightly above the speed of sound, moving outwards from the explosion at 1,150 ft (350.5 m) per second, it would take about 15 seconds to reach a person standing 3 miles (4.8 km) away, or to the general vicinity of The Oregon Health Sciences University.

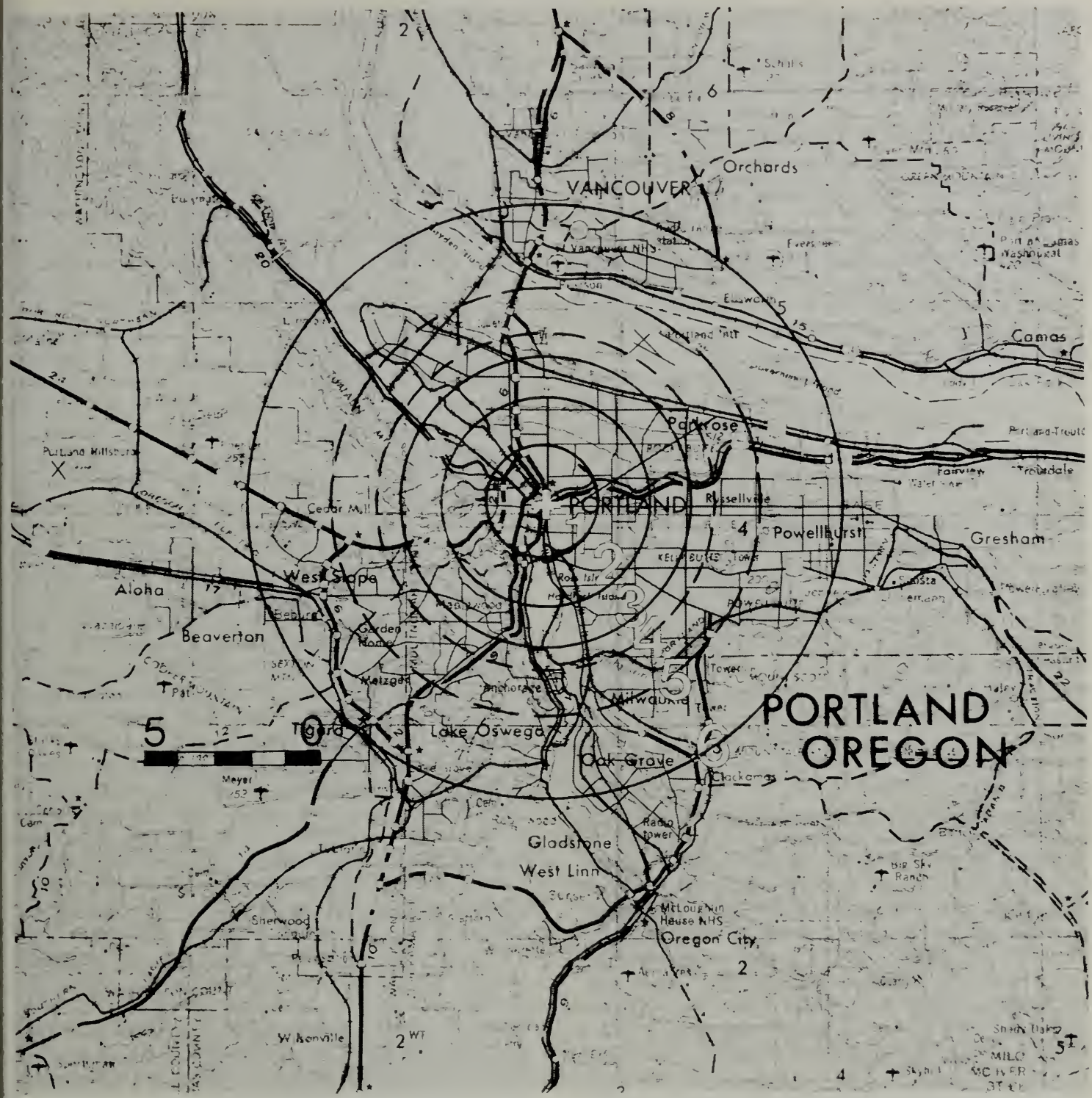
The pressure of the blast is measured in pounds per square inch (psi) above the atmospheric pressure. At two to three miles (3.2 to 4.8 km) from ground zero, the overpressure would be 9 psi, which is enough to flatten most buildings and cause lung hemorrhage and rupture in many exposed persons. Only seconds after the shock front passes, leaving a trail of destroyed buildings, uprooted trees and broken bodies, it would be followed by a reverse or negative-pressure phase. The combined effect of these two pressure phases would be first to squeeze or implode and then to expand or explode structures and human tissues. Winds in the range of 300 mph (482.8 km per hour) would follow the shock waves, causing additional damage by hurling debris, including broken glass, metal and human beings themselves through the air.

At Lewis and Clark College, we would see the flash—those looking directly at it being instantly blinded—but we would not feel a thing . . . for 20 seconds. When the shock wave hits it would be accompanied by winds strong enough to kill people by flinging them into nearby objects. High temperatures would continue to inflict third-degree burns on all those exposed. While these things are happening, the fireball would continue to burn in the sky. Soon, huge thick clouds of dust and smoke would darken the air as the mushroom cloud is sucked in and rises into the atmosphere. The darkness would be similar to that experienced by the victims of Mount St Helens' first eruption. Within one minute, in Gresham and Oregon City windows would shatter and roofs would be torn off houses. Damaged oil and gasoline tanks would fuel spreading fires.

As happened at Hiroshima, the individual fires would coalesce into a mass of fire, driven by the violent and turbulent winds, which would either become a fire storm or a conflagration—depending on the nature of the winds.[4] In a conflagration, prevailing winds spread a wall of fire as far as there is any combustible material to sustain it. In a fire storm, a vertical updraft caused by the fire itself sucks the surrounding air in toward a central point, and the fires converge in extreme heat, in the range of thousands of degrees, burning for days. A fire storm can increase the size of the lethal area five times.[5]

In either case, shelters would become death traps

*This format was developed and used by H. Jack Geiger, MD, in Physicians for Social Responsibility symposia in many different cities.



Circle	*Radius*	*Atmospheric Conditions*	*Effects*
+	Ground zero		
1	1½ miles	20 psi overpressures	All life and buildings pulverized.
2	3 miles	9 psi, winds 260 mph	Lung hemorrhage, third-degree burns.
3	4 miles	5 psi, winds 160 mph	Brick and frame houses destroyed, ear drums rupture.
4	5 miles	4 psi, 25 cal/sq cm	Spontaneous ignition of clothing and combustibles, fire storms likely, 50 percent of the people dead.
5	6 miles	3 psi, 12 cal/sq cm	Third-degree burns of all exposed skin, multiple trauma and lacerations.
6	8½ miles	2 psi	Exposed people burned and blinded by flash, all windows broken, second-degree burns, trauma.

Scale: 5 — 0 = 5 miles to ground zero.

Abbreviations: psi = pounds per square inch; cal/sq cm = calories per square centimeter.

Figure 2.—Area of Portland and surrounds that would be affected by a 1-megaton nuclear weapon air burst over Burnside Bridge.

because the fires consume all available oxygen as the temperatures in the shelters rise to levels of 1,500 degrees, roasting and asphyxiating the occupants. In Dresden during World War II, a fire storm was caused by intensive bombing with conventional weapons. The only persons who survived were those who fled their shelters.[6] The interiors of some of the shelters were so superheated that days later when they were opened and oxygen was allowed in, they burst into flame.

For greater Portland, it can be calculated that a 1-megaton airburst delivered during working hours would kill 466,000 people outright and leave 247,000 seriously injured out of a total population of 1.2 million. The initial casualties would be slightly less on a weekend. And, remember, present scenarios have cities multiply targeted. The later detonation of other bombs would immensely complicate the calculations of the blast, heat and radiation effects. Certainly the numbers of dead and injured and the area of devastation would be increased considerably.

For miles around the surviving injured would lie amidst the wreckage, suffering from second- and third-degree burns, fractures, lacerations and acute radiation sickness. Many would be partially or completely blind from the retinal burns caused by the luminous fireball. In the Marshall Islands when atmospheric testing of hydrogen bombs was conducted, focal retinal burns were found in animals as far away as 300 miles from the site of the explosion.[7] In addition, many people would be deaf. Threshold overpressures for rupture of tympanic membranes is 5 psi, which would occur anywhere within five miles of ground zero.[8]

Perhaps it would be optimistic to assume that there would be no further retaliatory strikes. What sort of medical response can be imagined in this awesome scene of blackness and destruction? In Portland, as in Hiroshima, Nagasaki and any other city, health professionals and medical facilities are concentrated in the center of the city. A major difference between this strike and that of Hiroshima is that in 1945 they had no warning. We may have as much as 30 minutes. In Hiroshima 90 percent of the physicians were killed within the first hours or day.[1(pp503-513)] On a weekend perhaps fewer would perish in the initial stages. But major hospitals would be gone. The one or two small remaining hospitals would be overwhelmed with tens of thousands of the dumbstruck, ambulatory injured who would find their way there. No transportation would exist to move the wounded through what streets could even be found.

"Imagine the familiar landscape turning suddenly into a sea of destruction: Everywhere smoldering banks of debris; everywhere the sights and sounds and smells of death. Imagine that the other survivors are wandering about with bleeding wounds, broken limbs, and bodies so badly burned that their features appear to be melting and their flesh is peeling away in great raw folds" (Lifton RJ, Erickson K: Nuclear war's effect on the mind. *New York Times,* March 15, 1982, p 14). The major immediate life-threatening injuries would be severe burns—tens of thousands of cases—which would overwhelm the burn treatment facilities of the entire country even in the ludicrous event that Portland alone was struck. There are only about 2,000 burn beds nationwide.

Physicians would have to deal with the injured without x-ray or other diagnostic facilities. They would face impossible decisions of triage with inadequate information. Radiation exposure would complicate this dilemma enormously, because the initial symptoms of radiation sickness—namely vomiting and bloody diarrhea—are almost the same regardless of what dose of radiation has been absorbed. At very high doses, those exposed would die in a matter of days from radiation-induced encephalopathy, preceded by delirium, seizures and coma. At lesser levels, persons may survive the initial symptoms, only to die within weeks of hemorrhage or infection due to bone marrow suppression. Some, who might have been saved with simple intravenous fluid therapy, would die of dehydration and shock. It will be almost impossible to know for sure who might survive, if given medical support, and who will die no matter what is done for them.

Sidel and associates[9] have calculated, using Boston as their model, that surviving doctors who spend ten minutes with each injured patient, working 20 hours a day, would need eight to ten days to see each injured person just once for only ten minutes, assuming that somehow the injured could be found and transported to a protected location.[9(p1139)] The assumption also is that surviving physicians would remain clearheaded and competent.

Again, we have not actually experienced such an event. But we have a great deal of information on human psychology under stress from which to extrapolate. Much important work has been done by Robert Jay Lifton in studies of atomic bomb survivors in Japan. "The suddenness and the sheer ferocity of such a scene would not give survivors any chance to mobilize the usual forms of psychological defense. The normal human response to mass death and profound horror is not rage or depression or panic or mourning or even fear: It is a kind of mental anesthetization that interferes with both judgment and compassion for other people" (*New York Times,* March 15, 1982, p 14). Certainly physicians and nurses would not be immune to this psychological devastation.

Here I must mention yet another major difference between nuclear attacks in the 1980s and those of 1945. The cities of Hiroshima and Nagasaki within days began to receive help from the outside world. The probability of nuclear war today remaining "limited" is quite small.[10] We cannot in our scenarios assume that there will be an outside world in any meaningful sense. Survivors will struggle in a meager and poisonous world in which everything that once mattered to them has been destroyed.

If areas to the south of Portland (such as Salem) were spared from an initial attack, I find it hard to imagine that doctors, nurses and emergency relief workers would come streaming northwards toward the

smoking remains of Portland. Even if they did, they would soon encounter thousands of dazed and injured refugees. There would certainly be enough of these people to quickly overwhelm the physical and psychological capabilities of the rural towns.

All of these projections assume that the physicians and nurses who survive would be willing to risk significant radiation exposure to help the wounded. Indeed, what is the ethical obligation of our profession in this nightmarish situation? Even to refer to scattered and confused persons as a "profession" is absurd in this setting. Would it not seem more important to doctors and nurses to be with their families—or to seek them in the rubble? Should physicians seek shelter in outlying areas where shelters may offer a chance of prolonging survival to some degree? Physicians claiming—as some have[11]—to be saving themselves and their skills, are also thereby negating the value of those skills, because while inside the shelter they can be of no use to those tens of thousands who are suffering and dying without comfort on the charred surface of the earth.

If some physicians and nurses of extraordinary altruism, or simply obsessively patterned behavior, were to set about to care for the injured, what would be the objectives of treatment? What could be done? It appears the most important medication would be narcotics to ease the pain of the dying, and yet these are not among the drugs stocked even in government shelters.[9(p1140)] Blood products, antibiotics and cardiovascular drugs would all be scarce or nonexistent. Diabetic persons would all finally die because there would be no insulin. The data can only lead to one conclusion: Beyond simple human solace, there can be no meaningful medical response in a nuclear war.

What about the fate of those who were in outlying areas where it may be possible to shelter oneself from the immediate effects? They would have to stay in those shelters for weeks before radiation levels allowed emergence for more than just a few minutes. Have provisions been made to treat those in whom acute radiation sickness develops once inside the shelter? How does one deal with severe protracted vomiting and copious bloody diarrhea in such a confined space? If there are deaths, and there will be, is it worth the risk of radiation exposure to remove corpses from the shelters?

Simple sanitation becomes impossible. Water would be a scarce resource. In the postattack period, survivors would be fortunate to have as much as the quart a day necessary for biologic survival. And there would be no guarantees that such water would be uncontaminated.

For those who emerge from their shelters, disposal of hundreds of thousands of human and animal corpses would be an unnerving and probably impossible task. A report by the Office of Civil Defense Mobilization states: "It is logical to assume that most combustibles as well as the dead on the surface within a 10 or 11 mile radius . . . will be either vaporized or incinerated through the resultant firestorm. . . . Intense radiation will prevent little more than heroic rescue in the 10 to 20 mile zone for several weeks. What cadavers might be recovered are those on the fringe of this area and upwind."[12]

This creates a situation that is ideal for the epidemic spread of infectious disease. Insects and bacteria are more radioresistant than humans, and will multiply easily in the wasteland of decomposing bodies. Radiation-induced immunosuppression among survivors will render them even more susceptible to infection. The lack of any organized social systems precludes anything resembling public health efforts. Abrams and Von Kaenel[13] synthesized the results of seven major studies to conclude that typhoid, dysentery (bacterial and viral), measles, hepatitis, plague and other infections are likely to kill at least 25 percent of those who survive the postattack period.

Finally, there are effects of nuclear weapons that call into question the survival of the earth itself as we know it. The National Academy of Sciences report of 1975[14] summarizes previous studies pointing to a consideration that makes survival a species question rather than an individual one. Megaton-range thermonuclear bombs release oxides of nitrogen into the stratosphere where they would promote the conversion of ozone into molecular oxygen. The ozone layer filters the ultraviolet rays of the sun, making it possible for humans to be exposed to the sun without incurring severe skin burns, blindness or—under milder conditions of ozone depletion—increased risk of skin cancer. The 10,000-megaton model used by the National Academy of Sciences projects a 50 percent depletion of ozone in the northern hemisphere and a 30 percent depletion in the southern hemisphere. Under these conditions it would be unsafe to be unprotected for more than 20 to 40 minutes. All mammalian eyes are at risk of blindness under such conditions—an eventuality that would mean utter and complete destruction of the ecosystem, for wild animals cannot survive without sight. Thermal alteration of the upper atmosphere could lead to global temperature shifts. The peak depletion of the ozone layer does not occur until well into the first-point attack year, and recovery could not be expected for at least six to eight years.

Nuclear weapons thus not only kill directly and violently but also kill indirectly and persistently by destroying the ecologic and social systems on which our individual lives depend.

Summary

To conclude, I want not to add still more to this analysis of horror, but to reflect on the significance of this kind of knowledge. All of what I have described is based on projections and probabilities. Some are open to more dispute than others, but all are attempts to use our extensive theorizing capabilities, together with the evidence of the use of nuclear weapons in war and in testing, to describe a range of probabilities for the unimaginable. With the expertise of physicists, physicians,

political analysts and others, we can construct possible scenarios—some of which you have just heard. Calculations may differ somewhat; some may prefer the 6,559-megaton model of the Federal Emergency Management Agency,[15] while others find the 10,000-megaton model of the National Academy of Sciences more credible. Population centers or industrial and military installations may be primary targets (with the understanding that there is significant overlap). Missiles as yet untested under actual war conditions may be more or less accurate. The rate and extent of ozone depletion varies depending on how many of the various-sized weapons are used in a given model. Weather conditions determine the characteristics of fallout distribution.

Much debate goes on today about such projections and even the facts on which they are based. As a physician I can only conclude that it is essentially irresponsible to point to those debates in supporting a claim of ignorance. We do not know it all, but we know all we need to know. For if any of what has been described as probable is even remotely possible, then there is no political reason on earth that can morally justify the continued uncontrolled existence of these weapons.

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The Survivors of Hiroshima and Nagasaki: Delayed Effects

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When the first atomic bombs were used in warfare over Hiroshima and Nagasaki in August 1945, history records that many thoughtful people in government and in science realized that a new era had been born. In the aftermath it was soon apparent that a major unplanned experience in human misery and an unplanned experiment in human radiation biology had taken place. With the Atomic Age at hand, it behooved us to understand the dangers of irradiation to humans. It was almost with a sense of diffuse curiosity, however, that the military commanders of the various units in the Pacific gathered a group of physicians and scientists and sent them to record the medical problems of Hiroshima and Nagasaki a few weeks after the bombings. Whether this early group of young scientists was well chosen or whether they simply rose to the enormous problems they found in the cities, they recorded acute radiation damage, defined many of the questions that needed addressing in subsequent years and became leaders in scientific medicine in the years ahead.

This early joint commission certainly highlighted that a serious, scientific, longitudinal and continuous biomedical survey of survivors was imperative. President Truman, in a proclamation, assigned to the National Academy of Sciences (rather than the then-named Atomic Energy Commission) direct responsibility for this huge epidemiologic research program. The academy, in collaboration with its Japanese equivalent, established the Atomic Bomb Casualty Commission (ABCC) which, in recent years as Japanese leadership has predominated, has become the Radiation Effects Research Foundation (RERF). The Atomic Energy Commission and its successor provided the physical studies of the bombs themselves and of radiation doses.

The tasks were staggering. The two bombs were different, the Hiroshima one being made of uranium and the Nagasaki one of plutonium. Their burst points over the two cities were calculated by "shadows" quite literally cast in stone, the shadows being images of structures that protected a stone or concrete structure from the immediate effects of nuclear heat. Multiple coordinates from such shadows defined the bomb-burst points in the air and established the plumb line to earth as the hypocenter. The power of the bombs was determined by simulations at test sites in the United States, the Hiroshima bomb eventually assigned about 12,500 tons of equivalent TNT (trinitrotoluene), and the Nagasaki bomb about 15 kilotons. The simulations at the US test sites proved that the bombs were too high above the ground to yield significant fallout, confirming early direct radiation monitoring in the two cities. Shielding of various sorts obviously attenuated the burn, blast and radiation effects, and at the US test sites concrete walls, Japanese houses, even paper shoji screens and simulated human bodies were tested for their shielding capacity, so that eventually distance from the bomb hypocenters plus attenuation by shielding could yield a human radiation dose. The first such tentative dose estimates became available in 1965 and are still being refined.

Aided by local censuses in the 1940s and a Japanese national census in 1950, a population of those who survived the bombings was established. Painstaking individual interviews established where people were located, who was with them, how they were shielded and the nature of their immediate and subsequent medical problems. This process proved painfully accurate, because the blinding light and blast had been imprinted on the memory of the survivors like a flashbulb photograph. The individual accounts, translated verbatim by ABCC translators and recorded as part of the shielding history, take on the elements of epic saga reminiscent of those in Hersey's *Hiroshima*.[1] Slowly, a population having known characteristics was assembled, and by 1957 this population was assigned into carefully defined cohorts of irradiated and nonirradiated survivors. Controlled clinical and epidemiologic studies could then be undertaken.

It should be recognized, however, that blast, fire and irradiation killed about 70,000 persons in Hiroshima and 30,000 in Nagasaki. Most of the survivors were beyond the intense zone of damage (about 1,500 m [0.9 mi] from the hypocenter), and those within that radius who survived blast, fire and radiation sickness

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numbered only a few thousand. The farther from the bomb burst, the greater the number of survivors and the lower the radiation dose. Conversely, survivors within 1,000 m (0.6 mi) of the bomb-burst points were shielded so that their body radiation dose is difficult to determine. With all of these problems of irradiation dosage, population ascertainments and large numbers, the medical findings of the survivors have been carefully and accurately documented.

Medical Findings

Congenital Damage

So little was known about radiation biology in 1945 that the survivors themselves, as well as the early medical scientists, expected anything and everything. Among the survivors, almost every physical or mental ailment was suspected of being bomb-related. Particularly, all congenital anomalies were termed "A-bomb disease." Early studies did confirm that most of the pregnant women in the latter half of gestation and those who had radiation sickness (defined as purpura, agranulocytic angina, hair loss and bloody diarrhea) did indeed abort. Studies of the offspring of pregnant women became of particular interest to the investigators, and the babies in utero during the first half of gestation were found to have an unexpected defect. Their skull bones fused prematurely, leading to microcephaly which in turn was associated with mild to moderate mental deficiency. This effect was related to dose or distance from hypocenter (or both), and there was some difference related to gestational age. These in utero irradiated children, both those with microcephaly and brain damage and those spared such sequelae, number fewer than 100 in both cities combined. They remain under close medical surveillance and so far other evident diseases have not developed in these children—now adults in their mid-30s.

Cataracts

The epithelium of the crystalline lens was known to be quite radiosensitive and early investigations found posterior lenticular cataracts. Some rapidly matured and required surgical extraction. Many persons, mostly those who received more than 100 rads, have early posterior cataracts that are readily discernible by ordinary ophthalmoscopy; these lesions have so far not worsened.

Genetic Damage

Genetic damage, particularly that causing somatic mutation, has been a known effect of irradiation in plants and animals, and such effects have been looked for continuously since 1945. The Hiroshima-Nagasaki genetic studies have benefited by the continuous scientific involvement and direction of Dr James V. Neel, Department of Human Genetics at the University of Michigan. The offspring of irradiated survivors have been observed carefully, and specific cellular and chemical probes have been applied to detecting genetic damage.

There is no doubt that atomic irradiation caused chromosome damage. In the late 1950s human chromosome examinations became available when it was found that cells in human blood divided when cultured with phytohemagglutinin. A few years later it was learned that human lymphocytes consist of long-lived cells that circulate for decades, presumably awaiting contact with an antigen for which they are programmed. These long-lived lymphocytes are the ones that divide when exposed to phytohemagglutinin, a substance now recognized as a nonspecific mitogen. Examination of the lymphocytes of atomic-bomb survivors in this manner indeed showed chromosome alterations resulting from the 1945 irradiation. The results were startling: up to 15 percent of lymphocytes showed some small chromosomal change, and the percentage and degree of abnormality were directly related to irradiation dose. Presumably such chromosomal damage has to date had no clinical effect. Similarly, isoenzyme studies show evidence of genetic damage, but again without as yet being clinically discernible.[2] Schull, Otake and Neel believe these detailed studies suggest that the genetic doubling dose is 156 rems, a value higher than that previously assumed.

The offspring of survivors (F_1 generation) are now almost a complete generation, with the oldest F_1 members older than 35 years of age, and the youngest direct survivors being of similar age. There are many second (F_2) generation members now in Japan. All three generations should continue under medical and epidemiologic surveillance to the extent feasible.

Leukemia

Because leukemia is a rare disease in Japanese, the appearance of a few patients with acute or chronic myelogenous leukemia in 1947 and 1948 heralded the first sign of malignant disease among survivors. Because leukemia is so uncommon and so clinically dramatic, ascertainment of cases in both Hiroshima and Nagasaki is probably quite accurate. The annual incidence of new cases peaked about 1952, and by 1980 had slowly declined to almost baseline levels.[3-5] The cumulative rate is highly dose-related, with perhaps a 50-fold increase in those receiving 200 rad. Although myelogenous leukemia is probably the most radiation-inducible malignant condition, the actual excess mortality from such a rare malignancy is about 100 patients.

Solid Tumors

From 1945 to 1960, all studies indicated that there was no excessive incidence of cancer in the irradiated survivors. Between 1958 and 1960 there was a definite excess in the incidence of thyroid nodules, all of which proved to be adenomas by biopsy, followed during the next 20 years by a slow accumulation of an excess in thyroid cancer of low-grade malignant potential.[4,5] As the years accumulate, an excess in the incidence of cancer of lung, stomach and breast has been proved. Now, more than 35 years after the event, the solid tumor rate is still increasing, with no evident abatement. Cancer deaths naturally increase with age, and

so far in these irradiated survivors the elderly seem more susceptible to radiation-induced lung cancer—in other words, radiation seems additive to whatever causes cancer. With breast cancer, the converse seems true, with more cancer in those who were irradiated as children or young adults.[4] Such a conclusion, however, is probably premature until the population has been followed even longer than 35 years. Persons who were then children in Hiroshima and Nagasaki are now adults in their middle years and are just approaching the natural acceleration of mortality from malignant disease. Up until 1978 there were fewer than 200 excess cancer deaths attributable to irradiation.[5] From the data, however, it seems that a dose as little as 10 rads is carcinogenic, making a so-called safe dose threshold unlikely.

Psychologic Heritage

Psychologic damage is a known concomitant of disasters, whether natural or manmade. The unique feature of the Hiroshima-Nagasaki disaster is the continued daily reminders to survivors. Being a living statistic of the sort described here raises constant anxiety. All of the little complaints and illnesses of life take on a slightly sinister aspect. The possibility of genetic damage has interfered with the normal processes of marriage and parenting. With all these added stresses, the remarkable human attribute is that survivors and their nonirradiated friends and neighbors (as controls) continue to cooperate in the medical and scientific effort so that some day all the delayed effects of irradiation in Hiroshima and Nagasaki will be known. To the many of us who have worked in Hiroshima and Nagasaki, the gentle forbearance of the people has been an uplifting example, and a further goad to do what we can to prevent the "ultimate Hiroshima."

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The Last Traffic Jam: Psychologic Consequences of Nuclear War

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Only humans, it is said, know death. God, the Bible relates, cast Adam and Eve out of Eden, confronting them with the awful truth: "Dust you are, and to dust you shall return." The human quest for meaning in life, before the 1940s, was to reconcile the beauty and transience of life with death's mystery; this was also the ultimate task of religion. Knowledge of death can permeate and poison life, or it can raise our sights from petty personal gain to a higher and transcendant meaningfulness.[1]

With Hiroshima and Auschwitz, death acquired new implications, forcing mankind to face not only individual death, but also the absurdity of collective extinction. While individual death can seem at times a gift of rest, as Hamlet dreams, or almost an art form, as per Sylvia Plath, collective self-annihilation is as new a phenomenon to humankind as the knowledge of individual death was to Adam and Eve. Just as Adam and Eve's disobedience to God in the biblical story brought about the awareness of individual death as our inevitable fate, now humanity's collective decision to violate the fundamental moral tenets of every religion threatens permanent extinction and an end to the evolutionary experiment called humanity.

The mind recoils from this confrontation with extinction and seeks to dull the painful truth with denial or even illusions of survival. The Jews in the ghettos of Eastern Europe trudged to the cattle cars, for the most part ignoring fearful rumors and choosing to believe the Nazi leaders who told them they were being resettled for work in the occupied eastern territories. Instead, of course, they were sent to death camps. Similarly, many people prefer to believe reassurances of the chances of surviving nuclear war, rather than face the terror of possible nuclear annihilation.

As the awareness of individual death tends to render individual life meaningless, so the prospect of absurd and grotesque mass suicide threatens to render society meaningless. Victor Frankl[2] relates that those who survived the Nazi death camps often did so because they possessed an investment in the future, an intrapsychic need to fulfill some task before surrendering to the relatively attractive option of death rather than continued torture. "The prisoner who had lost his faith in the future—his future—was doomed. With his loss of belief in the future, he also lost his spiritual hold; he let himself decline, and became subject to mental and physical decay."[2] Now, the prospect of species annihilation overwhelms us and saps the creativity, ingenuity and capacity for nurturance that is everyone's birthright, because the world itself seems to have no future.

From the moment that this threat is recognized, individual lives can be poisoned. Fear and anxiety may become encrusted deep within the psyche and, like an abscess, "draw off" our ability to love and work, resulting in a subtle, chronic enervation. Alternatively, anger and a retreat to primitive patterns of competition, nationalism and paranoia may ensue. As Yeats put it, "The best lack all conviction, while the worst are full of passionate intensity."[3] Even if nuclear holocaust were prevented forever, there remains the psychologic malaise resulting from the fear of extinction, and the fear of our immense power over nature and tenuous control over our own aggressions. Society becomes emaciated by a lack of social values. Just as individual persons may succeed in transcending death, through spirituality or creativity, societies will languish until a moral decision is made to cherish life and to reject genocide.

We are now in the first phase of a war that really would end all wars, and the psychologic consequences of this first phase are at once to worry and also to be susceptible to misinformation that feeds the child inside of all adults, that child who seeks reassurance that somehow the adults have the child's security in mind. Psychologic solutions to this intolerable tension may be the paralysis of despair, or suicide. Dr John Mack, a psychiatrist at Harvard, studied more than 1,000 adolescents in Massachusetts for their attitudes toward nuclear war. He found that most of these children were already deeply disturbed by the omnipresent threat; they also evidenced cynicism, sadness, bitterness and a sense of helplessness. Some were literally unable to plan ahead for families or careers in any long-term sense.[4] In a similar study of "stoners," adolescent drug

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abusers from Milpitas (California) High School, Elizabeth Kaye found that fear of impending nuclear war was expressed by "every single teenager" she met, regardless of how otherwise uninvolved they were. One child said, "We're not going to last much longer." She burst into tears. "I'm sorry, but I get so upset. I think of all the things I'll miss" (*Seattle Post-Intelligencer,* April 11, 1982, pp B1,3). Both Mack and Kaye attribute heavy drug use and hedonistic behavior in these teenagers to a loss of faith in the future.

Alternatively, many people have made a shocked retreat from reality, to a denial that verges on being delusional, that somehow nuclear war would not be so terrible after all. Foremost advocates of this delusion are the self-styled survivalists who claim that human beings are not social animals after all, but rather are capable of meaningful survival even in the absence of societies. Additionally, certain officials of governments in Russia, England, other European countries and America claim that civil defense, not prevention, is an answer to the nuclear threat. The notion of the individual survival instinct rings true with the popular saying—which made sense in long eons of evolutionary testing—that "when the going gets tough, the tough get going." Flight is an understandable primitive response to terror. However, reality changed fundamentally with the escape of the power of the sun and the stars to earth, and it is ludicrous for official government agencies to respond to this threat with as much adaptive reasoning as an ostrich that buries its head in the sand.

In the United States, the Federal Emergency Management Agency (FEMA) is the foremost proponent of "ostrichism." While in the past one could say that "Civil defense is the opiate of the people," the frightening change now is that these officials actually seem to believe themselves. FEMA claims that with three to eight days of warning before a nuclear attack, through mass evacuation, up to 80 percent of the American people and substantial parts of industry and the economy could be saved in an all-out nuclear war (*Los Angeles Times,* January 15, 1982, p 1). Medically, socially, economically and rationally this makes no sense. The detonation of even 20 percent of Soviet arsenals on US cities and industries could destroy 110 million people (55 percent of the US population) and 70 percent of the nation's industry.[5(p102)] Yet this magnitude of destruction is completely out of the range of human experience, and the mind rebels at the thought. The myth of survivability seems more attractive, with the result that the world is sliding rapidly toward nuclear war, rather than a massive revulsion at the concept of nuclear annihilation and a retreat from the abyss.

Perhaps only a shock can break through this denial process. We must learn to stretch the imagination—that is, to think the unthinkable, in Herman Kahn's words—to be able to grasp the reality of 50,000 stars falling to earth. Robert J. Lifton has said, "The only problem with shelters is getting into them, staying in them, and getting out of them."[6] Examining the psychologic sequelae of evacuation, sheltering and survival in a postattack world may be one way to stretch the imagination, so that never again will humans queue up in orderly lines, waiting patiently for their own annihilation.

Tension Grows

Mounting international tensions will provoke immediate internal effects in the United States that will add to the pressures on national leaders to act, perhaps with a preemptive first strike. Earliest effects will consist of increasing individual resistance to participation in society, as preoccupation with anxiety and individual and family survival grows. The primary result is economic slowdown. Anxious people work more slowly, less accurately and with more distraction. As international anxiety rises, citizens will be less likely to buy houses or cars, invest in retirement plans, save money or even reproduce. Altruistic behavior decreases as people feel less secure themselves and as they perceive less opportunity for reciprocation.

Evacuation

As tension mounts, there will be increasing numbers of voluntary, unplanned evacuations. The evacuation of the area around Three Mile Island showed that even without governmental instructions, many people will evacuate their homes, from the fear of nuclear catastrophe. In Pennsylvania 145,000 people were evacuated from an area of 706 square miles (1,829 sq km) surrounding the damaged reactor. Among the reasons given for leaving were the dangers of the situation (90 percent), to protect children (61 percent), because information was confusing (83 percent) and to avoid the danger or confusion of a forced evacuation (76 percent).[5(pp362,363)]

The effect of voluntary evacuation will be a further slowdown of the economy. Businesses, factories, hospitals and schools will falter, and possibly close. The reliability of the monetary system will be questioned and credit cards and checks may lose value first. Massive withdrawals of cash from banks may force banks to close. Moreover, the evacuees may face hostility from people in the host areas, when money loses its meaning and they wish to stay on as guests.

As people watch their neighbors, friends and colleagues voluntarily evacuate, insecurity and fear would spread rapidly and chaos and panic might ensue. The President might be forced into proclaiming a national evacuation program, to try to forestall the chaos of the spontaneous flight from the cities. Of course, the start of a national evacuation program might trigger the start of war, because spy satellites would quickly show the movements of populations, and each side would worry that the other side was planning a first strike.

What would happen in the United States if suddenly the air-raid sirens started to blow and the harsh tone of the emergency communication system interrupted and terminated radio and television shows throughout

the land? Today's young adults grew up in the 1950s when civil defense drills were commonplace, and most of them have a hidden, inner fear of nuclear war. The sound of the sirens might well reduce them to the psychologic state of terrified children, feeling as they did during the air-raid drills of the 1950s, afraid that their nightmares were about to become real. Panic is a small word to describe the engulfing fear of the flames and fire.

Amid the panic, concern for family members and fear of separation would predominate. In most urban centers, parents usually work at considerable distances from their children's schools and day-care centers. The sirens would send both children and parents into further panic, and any prediction that authorities try to make of traffic patterns would be disrupted by desperate parents and wives and husbands trying to locate one another. During the Three Mile Island accident, children were frightened by seeing other children and teachers removed from school in tears. Children were abandoned in locked houses, left to fend for themselves. Some schools were evacuated as a whole, without informing parents.[5(p367)] Fear of separation would be heightened by the uncertainty of the time of the attack, and fear that the separations would be final.

The Three Mile Island evacuation demonstrated an enormous distrust of government information and plans. With the threat of imminent nuclear war, who would patiently wait his or her turn for evacuation? FEMA has devised schedules for evacuation, neighborhood by neighborhood, but who could resist the impulse to cheat, to try to sneak in line on the freeways and leave the high-risk areas quickly? Traffic jams would be unprecedented as some persons rushed for the evacuation routes while others tried to return to the cities to rescue relatives. Even in peacetime, large traffic jams try the patience of many normal people and turn others into beasts behind the wheel. In this last traffic jam, angry and aggressive behavior would be predicted, particularly in response to delays. For example, an unfortunate family that runs out of gas on a narrow road might be the victim of vicious attempts to throw the car off the road rather than altruistic attempts to share gasoline.

Civil servants have no monopoly on courage, devotion to duty or altruism. Neither do they have notable excesses of the same. Would the call to protect one's family and self be less strong on a bus driver or policeman than on a businessman or florist? Probably not. Then, as the evacuation progressed, vital community services such as police, ambulance, transportation and health care services would collapse. The question of the evacuation of hospitals poses a particularly difficult dilemma. Which of the sick and injured would be evacuated, and would health care personnel abandon their own families and self-interest to take care of those who could not be evacuated? In Seattle, a specific person is apparently designated to go to the zoo when the attack is announced, to shoot the heads off the poisonous snakes, so that they would not pose a risk to the survivors. Is there someone in each hospital who has similarly been designated to euthanize the ill, rendered terminal by their immobility, when it is time to evacuate?

It is possible that many people would defy the evacuation orders and choose to die in their own homes with their families, rather than face the risks and insecurities of evacuation. An example of such behavior was shown by Harry Truman, the elderly innkeeper at Spirit Lake, Washington, who chose to ignore the scientists' warning of the eruption of Mount St Helens in 1980 and died at home in the mudslide. A common sentiment is, "When the bomb goes off, I hope I'm at ground zero." Fear of radiation sickness, starvation and riots may be greater than the fear of being vaporized in a microsecond and many people, anticipating such an end, may choose to stay home. Mass and family suicides are also likely, in the manner of the Jonestown (Guyana) massacres; parents may choose to kill first their children and then themselves, rather than live with the intolerable fear of being separated, killed or maimed.

The Shelter Period

An all-out countercity nuclear war with the Soviet Union would probably begin and end very quickly, with the detonation of approximately 20,000 megatons of explosive power in a short period. It is estimated that 10,000 megatons of bombs would fall on the United States, with approximately 2,000 bombs aimed at military and strategic targets and 4,000 at cities. The Arms Control and Disarmament Agency estimates that 80 percent of cities with populations of 25,000 or more are targeted.[7] The US Office of Technology Assessment estimates that between 20 million and 160 million people will die immediately,[8] out of a total population of 240 million. The remaining population would probably be sheltered in makeshift shelters in rural areas, except for high-ranking government officials who are designated to go to well-equipped blast shelters buried deep in the mountains. Most of those in shelters would face enormous difficulties, depending in part on the sophistication of the shelters.

The initial shelter problem would be to determine who gets in, because even primitive shelter space is extremely limited. Unfortunately, many designated shelters are similar to the one in Shelton, Washington, which is merely a long, narrow concrete tunnel under the Shelton Correctional Facility that could accommodate some 6,000 persons under crowded conditions. About 65,000 people from Thurston County are scheduled to go to Shelton. There are about 10,000 residents in Shelton alone. Who is to say who gets into the shelter? Those who do not get in will be advised to dig deep holes, cover the holes with a door and some dirt and crawl beneath the door. Deputy Undersecretary of Defense T. K. Jones, in an interview reported in the *Los Angeles Times* (January 18, 1982, p 1) states, "Everybody's going to make it if there are enough shovels to go around. . . . it's the dirt that does it." Perhaps another aspect of this strategy would be to

encourage people to dig their own graves, to minimize problems of disposing of the human corpses.

While underground shelters are somewhat protected from blast, fire and fallout, many have no provisions for lighting and have minimal ventilation. Underground evacuees may be huddled in the dark with minimal food, water and communication. However, many rural shelters are not underground. For example, many traffic tunnels are designated fallout shelters. Those in aboveground shelters will still lack food, water, toilet facilities and air filtration and moreover will have only minimal fallout protection. Only a few shelters will have radios, and because one effect of nuclear explosions is to disrupt communication systems, most shelters will be isolated from the world outside. Fear of an incipient attack and speculation about the fate of the world will produce further feelings of demoralization, helplessness and apathy.[9]

Most shelters will lack means to measure radiation levels, so there will be chronic anxiety about the invisible contamination of radiation sickness. Both at Three Mile Island and Hiroshima, hypochondriacal complaints mimicked the prodromal symptoms of radiation sickness, which are weakness, headache, nausea, anorexia, vomiting and lethargy. It will be impossible to tell who is going to die of radiation sickness in hours, days or weeks, and who will recover from the low doses of radiation or hypochondriacal symptoms. The care of the sick will be complicated by the problem of disposal of the corpses. A physician described a scene in a hospital in Hiroshima:

> Patients who could not walk urinated and defecated where they lay. Those who could walk would feel their way to the exits and relieve themselves there. Persons entering or leaving the hospital could not avoid stepping in the filth, so closely was it spread. The front entrance became covered with feces overnight, and nothing could be done, for there were no bedpans, and even if there had been, no one to carry them to the patients. Disposing of the dead was a minor problem, but to clean the rooms and corridors of urine, feces, and vomitus was impossible.[10(p12)]

The Crisis Relocation Plan from the Massachusetts Civil Defense Agency claims that

> while no one can guarantee perfect behavior in such an unprecedented situation as crisis relocation, the judgment of those who have studied peacetime and wartime evacuations is that constructive and law-abiding [behavior?] would be predominantly, and indeed overwhelmingly, the case. In an emergency, people tend to be jolted out of their normal routines and patterns, and many people go out of their way to help others.[11]

This optimistic, cheerful expectation of human behavior contrasts remarkably with the reported behavior of the Hiroshima survivors, who were generally too demoralized and dazed to respond to the needs of any but immediate family members. The Boat People of Cambodia suffered stresses analogous to shelter inmates: isolation, hopelessness and despair complicated by danger, demoralization, thirst, dehydration and starvation. There are reports that some refugees killed and ate young children so that the adults might survive (*Time,* January 11, 1982, pp 32, 61).

FEMA documents compare the behavior of persons evacuated from the scene of natural disasters such as hurricanes with projections of human behavior during evacuations preceding nuclear war. It may be true that people can be evacuated from hurricanes with minimal social or psychic disruption. Nuclear war, however, is fundamentally different from natural phenomena for three reasons. First, nuclear war is beyond human experience and has only two precedents, Hiroshima and Nagasaki, both of which connote intense fear. Humans habituate remarkably quickly to stress when it is predictable. For instance, the evacuation of the region surrounding Mount St Helens in 1980 was frightening and stressful. By contrast, the evacuation of the same area in March 1982 was relaxed, and Mount St Helens' jokes were commonplace. Because nuclear war is unfamiliar and portends to be catastrophic, people would be unlikely to respond with aplomb. Second, in the case of a hurricane, volcanic eruption or major hotel fire, the event is time limited, affects a specific region and there exists an outside world that can mobilize its resources to aid the victims. In a nuclear war, there will be no outside and no anticipated return to ordinary existence. The duration of the crisis will be indefinite. Third, radiation offends human sensibilities because it defies the senses. The fear of contamination, radiation sickness, cancer and genetic mutations is as intense as the fear of death, and far more mysterious. No natural phenomenon excites such anxiety.

Postattack Survival

Optimistic projections of the shelter period estimate that perhaps 10 percent of Americans will survive. It is difficult to imagine the world that they may face. No one knows whether or not the world will be darkened for a few years, following the deposition of enormous amounts of dust in the stratosphere. Whereas long-term climatic changes may not occur, just a single year of darkness may destroy most plant and animal life on earth. Alternatively, the world might be a brighter one, far brighter because the ozone layer could be depleted, and ultraviolet rays from the sun may pour through the atmosphere, burning plants and blinding animals and humans.

Each survivor will be confronted by unending problems of determining what to eat and what to drink, because the earth will be contaminated with long-lived radioactive isotopes that may be a source of increased radiation for every living thing on earth for thousands of years. Survivors might feel rather like King Midas: everything they touch, eat or drink will have varying levels of contamination.

Most survivors will have lost most, if not all, family members. Friends and foes alike will be dead. There will be millions of rotting corpses, both animal and human, and the constant threat of infections and plagues. The eeriness and "death immersion" of the postattack period is illustrated by this doctor's account of Hiroshima:

> There were no mosquitoes. This was strange because they were usually very numerous in the park at night. I could hear the croaking of frogs, and thought this strange, because why should

they survive when the carps and the eels were dead. At intervals, swishing sounds and soft thuds occurred nearby. These eerie sounds, I discovered, were made by birds, who from time to time lost their perch in the trees above, and fell to the ground dead.[12]

Those who survive will not dare return to their cities, which will have become radioactive mausoleums. The evacuation will in no way resemble a two-week vacation in the country, followed by the return to a life that was in any way similar to the time before the war. Survivors will have lost their property, their livelihoods, their family homes and probably their families as well. Evacuation host areas are far from population centers precisely because they lack water, or have inhospitable terrain. A severe water shortage will stifle attempts at rebuilding cities or reestablishing agriculture. Within a week, the survivors will travel backward in time, from the age of computers to the stone age.

These poor, weak, frightened persons will have no time to consider whether life has meaning. Rather, they will probably drag through their remaining days as did the inmates of Auschwitz—demoralized, dehumanized and oblivious. Will these walking corpses also lose the capacity to form relationships with one another? Will they dare to make friends or alliances? Will anyone in the postattack period dare to fall in love or to reproduce, knowing that everyone has been exposed to radiation? The most basic meaning in life is continuity through successive generations, usually through parenthood but also through teaching and creating new forms that will endure beyond the scope of individual survival. With the end of love will come the end of meaning.

Conclusion

There are fundamental differences between the quest for meaning in an individual life faced with individual death and the quest for social meaning in a world faced with nuclear war. Individual death is inevitable. Collective death is not. Individual death is a certainty that may be transcended spiritually or creatively. Nuclear annihilation is a problem created by humans and requiring human solutions; otherwise, there will be no opportunity for transcendence. It is the height of selfishness to assume a fatalistic approach to collective extermination, as though with the death of the self, the deaths of all others lose meaning.

Yet, by breaking through the denial and fatalism and becoming involved in an active way on behalf of our children and the planet, we have an opportunity to find enhanced meaning. We can show our children that we love them enough to grow up ourselves and to shoulder this awesome responsibility.

Let me close with a story. A man who is newly active in the peace movement told me that one day his son's teacher asked his class what they thought about nuclear war. Fourteen of the 7-year-old children felt that nuclear war was coming, and they were terrified. Only the man's son felt secure. When asked why, the boy stated, "I know that there won't be a nuclear war because my daddy goes to meetings all the time to prevent it."

Who among us can deny children this hope?

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Medical Progress

Physiology and Pharmacology of Hypothermia

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Homoiothermic organisms react to hypothermia by shivering and thermogenesis to retain their euthermic state. This reactive homeostatic mechanism recruits a strong sympathetic response, which must be suppressed by anesthesia and adjuvants during induced hypothermia. Below 30° C there is significant neural and organ depression associated with cold narcosis. Cardiac arrhythmias and ventricular fibrillation are grave developments when the core temperature is below 28° C. Proper cardiopulmonary support must be instituted in a patient who has induced or accidental hypothermia at these severely hypothermic levels.

Although clinical hypothermia is used to protect the brain and the heart from ischemic insults during an operation, it induces a complex array of physiologic changes in the body that must be appreciated so that optimal care may be provided to a patient.

Hypothermia induces a complex array of physiologic changes that in turn cause abnormal responses to drug administration. An enormous amount of information has been accumulated in the past three decades on the effects of cold on living organisms, but it is not the purpose of this report to exhaustively review other published articles on this subject. Instead, a brief historical note of medical interest, followed by some selected topics of hypothermic physiology and pharmacology, will be presented. I have intentionally taken a simplistic approach to a complex topic in the hope of providing the reader with some useful information about hypothermic patients.

Background

The analgesic and hemostatic effects of cold have been recognized throughout the ages. Hippocrates used snow and ice to check hemorrhage. "Refrigeration" anesthesia was used during the Renaissance. Baron Larrey, Napoleon's surgeon-general, took advantage of the cold battlefield to carry out surgical repair on hypothermic soldiers without additional central nervous system depressants. Following the introduction of ether in 1846, it was recognized that topically applied ether can produce regional anesthesia by freezing tissues. The use of ethyl chloride as a topical anesthetic soon superseded that of ether and is still being used today.

The concept of total body hypothermia was tested by William Cullen in 1755 when he attempted to cool small animals to a state of suspended animation and in 1766 when John Hunter tried unsuccessfully to revive carp after a period of induced freezing.[1] The application of hypothermia to clinical problems in medicine was pioneered by Smith and Fay,[2] who treated cancer patients by reducing their rectal temperature to 24° to 32° C (75° to 90° F) for up to five days. Regression of malignant growths was observed, especially when the cold was applied locally as with carcinoma of the cervix; but in general there was no permanent reversal of the cancerous process. In 1941 Talbott[3] used prolonged total body hypothermia as a means of administering shock therapy to psychotic patients, but with little success and with two cardiac deaths. McQuiston[4] in 1949 advocated total body cooling during operations in children with cyanotic heart disease, but his rationale for the treatment was to reduce oxygen demand more by counteracting hyperthermia than by inducing true hypothermia. The current clinical application of hypothermia stems chiefly from the laboratory observations of Bigelow and associates,[5-8] who suggested the feasibility of complete circulatory arrest to permit an intracardiac operation in a bloodless field. The reduction of oxygen consumption is proportional to the reduction of cellular temperature. The tolerance of tissue to hy-

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poxia is therefore increased during clinical hypothermia. Although surface-induced hypothermia is only used to a limited extent in surgery today, in a selected group of neonatal cardiac operations, the use of induced regional or total body hypothermia has permeated to a variety of surgical procedures where tissue viability might be improved. For the purpose of communication, clinical hypothermia can be divided into (1) mild hypothermia, 32° to 35° C (90° to 95° F); (2) moderate hypothermia, 26° to 31° C (79° to 88° F); (3) deep hypothermia, 20° to 25° C (68° to 77° F); and (4) profound hypothermia, 14° to 19° C (57° to 66° F).

Physiologic Effects

Humans need to maintain a body temperature close to 37° C regardless of the ambient conditions, in contrast to a hibernating animal that goes into a deep sleep from which it can be aroused with a subsequent rise in temperature. The thermoregulatory mechanisms of the hibernating animals are quite different from those of humans; thus, the physiologic changes of hibernating animals during hypothermia cannot be used as models for clinically induced hypothermia. The disparity of published laboratory results stems from the following: the lack of a standard for normal physiology during hypothermia; the application of different experimental conditions, that is, types and depth of anesthesia, adjuvant drugs, spontaneous versus controlled ventilation, control of acid-base changes, rate of cooling and so forth, and the use of different animal species. Aside from the major differences observed between hibernating versus nonhibernating animals, it can be generalized that smaller animals tolerate cold better than larger animals.

The initial response of a homoiothermic organism to external cold is to generate body heat from shivering and to elicit a strong sympathetic response to resist against lowering of the body temperature. Vasoconstriction is profound; oxygen consumption increases; the respiratory rate accelerates; the heart rate, stroke volume and cardiac output increase, and the blood pressure rises. In the inhumane trials carried out by the Nazis at Dachau, in which prisoners were immersed in water at temperatures of 2° to 12° C, reportedly there was initially violent shivering, succeeded by intense muscle rigidity; consciousness became clouded at a rectal temperature of 31° C, and both muscular rigidity and shivering ceased at rectal temperatures of around 27° C.[9] These initial responses to maintain homeostasis are detrimental to a patient in whom hypothermia is induced. Thus, the appropriate administration of anesthetics and adjuvants is important to suppress these responses, to maintain a stable cardiovascular system and to insure a smooth intraoperative course. "Cold narcosis" supervenes at temperatures below 30° C, so that the requirement for central nervous system depressants is greatly reduced.

Metabolism

Total body metabolism, as reflected by lowering of oxygen consumption, is proportionally reduced with

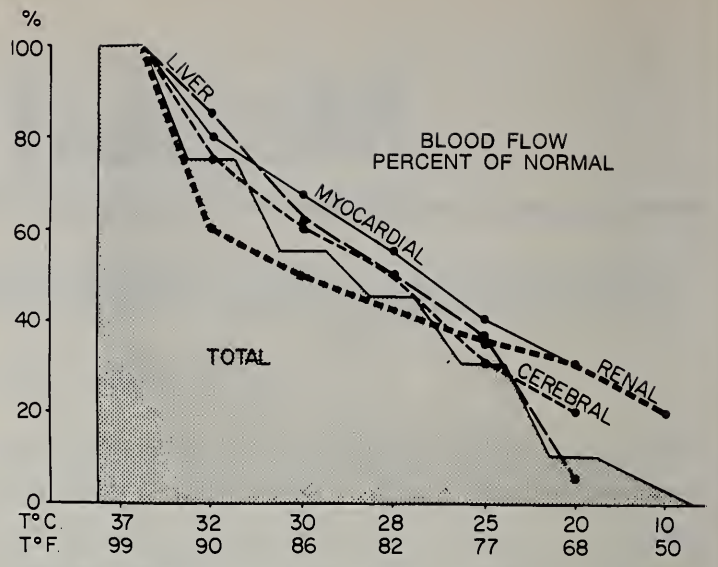

Figure 1.—Blood flow to the organs reduces with progressive hypothermia. The shaded area is total flow. The heart, liver and brain maintain a higher level of flow in comparison with the kidneys to 27° C. However, at 25° to 20° C renal and myocardial blood flows are sustained at 20 percent to 25 percent of normothermic levels whereas cerebral and hepatic blood flow show greater decreases. (Reproduced from Clinical Hypothermia by E. Blair. Copyright [1964, McGraw-Hill]. Used with the permission of McGraw-Hill Book Company.)

progressive hypothermia administered under anesthesia. Whether this fall in oxygen consumption is linearly or exponentially related to the drop in body temperature is still controversial. From a practical viewpoint there is roughly a 6 percent fall in oxygen consumption per degree-Celsius fall in body temperature within the range of hypothermia used clinically today.[10] The earlier estimates suggest that oxygen consumption by dogs is reduced to 50 percent of normal at 30° C[7] and 16 percent of normal at 23° C.[11] More recent data obtained from direct measurements of oxygen consumed by dogs from a closed anesthetic circuit show a 50 percent reduction of oxygen consumption at 28° C and a 75 percent reduction at 20° C.[12,13] These changes obey, in general, van't Hoff-Arrhenius's law, which states that the rate of chemical reaction is doubled for each 10° C rise in temperature or halved for each 10° C fall in temperature. The measurement of total body oxygen consumption to reflect the metabolic state of the body is analogous to the measurement of arterial blood pressure to reflect the circulation. Both are the net result of multiple organ responses.

The extent of the reduction in metabolism of individual organs would not be the same even if all the organs in the core were reduced to the same temperature. At normothermia, oxygen consumption is the highest in the kidney, which consumes 8 percent of total body oxygen while representing only 0.5 percent of the weight of the body.[14] The liver, heart, brain, skeletal muscle and skin follow a descending order of oxygen consumption. However, renal oxygen consumption during hypothermia to 32° C is most rapidly reduced in comparison with the other organs, with a parallel de-

crease in blood flow during the same period of temperature reduction (Figure 1). Thus the body perceives the kidneys as the most dispensable organs for maintaining homeostasis. Indeed the kidneys are also the first organs to be deprived of blood supply during hemorrhage, hypoxia and general anesthesia. Urinary output is an important clinical reflection of organ perfusion.

Carbohydrate, Protein and Fat Metabolism

The metabolism of carbohydrate during hypothermia is reduced. This is reflected by hyperglycemia proportional to the level of cooling.[15-20] Many factors can contribute to the increase in blood glucose. Inadequate protection from the stress of induced hypothermia can promote glycogenolysis and gluconeogenesis from the stimulation of adrenal catecholamines and glucocorticoids. In the presence of adequate anesthesia hypothermia can still cause defective carbohydrate metabolism. Insulin activity is greatly reduced.[15-17] Renal clearance of glucose is compromised.[18] Enzyme hexokinase, which is inhibited by cold, may fail to catalyze hexose transfer across cell membranes, causing a general reduction in liver function.[19] Glycogen stores in the liver are reduced.[20]

There is a dearth of information about protein and fat metabolism. In general plasma proteins are inconsistently affected during induced deep hypothermia in dogs.[21] A depletion of body stores of fat, carbohydrate and protein progressively worsens and is related to the release of cortisol, catecholamines and other stress hormones, especially during accidental hypothermia.[22]

Water and Electrolyte Balance

Changes in extracellular cation concentrations are not of major significance during mild to moderate hypothermia.[23-26] The plasma potassium level in general is reduced without loss of potassium from the body. Under normothermic conditions, general anesthesia and muscle relaxants can also induce hypokalemia in dogs.[27] Patients under general anesthesia show reduced renal excretion of potassium.[24,25] Cellular loss of potassium during deep hypothermia has been implicated in the genesis of cardiac rhythm disturbance[23,28-30] observed at temperatures below 25° C (see the more detailed discussion of cardiovascular metabolism below). Plasma sodium, calcium and chloride concentrations do not change appreciably until the temperature is below 25° C.[23] Hyperkalemia during deep hypothermia is an ominous sign and generally indicates tissue hypoxia.[26]

No significant alterations in body fluids are observed in dogs anesthetized for a short time at 27° to 20°C.[23] However, prolonged cooling at temperatures below 25° C increases cellular water production and decreases plasma volume.[31] It is generally believed that fluid is also sequestered in capillaries during hypothermia; the addition of hemoconcentration and increased blood viscosity to an already compromised circulatory state results in a serious problem for perfusion.[22,32]

Respiration

Hypothermia initially stimulates spontaneous respiration but then ultimately depresses it. Except for the early transient increases observed during the initial cooling period,[6,33] a close relationship exists between the fall in body temperature and the decrease in the respiratory rate and depth.

Cessation of spontaneous respiration is observed at 24° C during experiments with dogs.[33] Respiration must be supported during induced deep hypothermia. But hibernating animals and some accidental hypothermic victims can maintain spontaneous respiration appropriate to the need for carbon dioxide elimination by the lungs. Thus the importance of anesthetic depression of respiratory centers during induced hypothermia has been well recognized.[33-36]

Both physiologic and anatomic respiratory dead spaces are increased during hypothermia. The mechanism is probably cold bronchial dilation.[35] Alveolar dead space is unchanged. The pulmonary exchange of both oxygen and carbon dioxide is not significantly affected during hypothermia.[10] The reduced ventilation is due to a reduction of metabolic requirement and a direct effect of cold on the nervous system. The reduction in oxygen consumption is accompanied by a reduction in carbon dioxide production and direct cooling depresses the entire nervous system including the respiratory centers.[33] Maximal sensitivity of respiratory centers to carbon dioxide stimulation is around 34° C (94° F), whereas the response to hypoxic drive is maintained even at deep hypothermic levels.[37] In animals both carbon dioxide and hypoxic stimulation for respiratory drive are largely gone at 20° C.

Cardiovascular

The effects of hypothermia on the cardiovascular system have been widely studied because the application of clinical hypothermia in modern times has focused on cardiac surgery and myocardial preservation. Again, if the initial sympathetic response to induced hypothermia is suppressed by anesthesia or drugs, there is a proportional decrease in cardiac output, heart rate and mean arterial blood pressure, with little change in stroke volume and an increase in peripheral vascular resistance.[8,11-13,26,32,38] The reduced cardiac output is primarily the result of a slowed heart rate, which slows to about 50 percent of normothermic levels at 28° C and about 20 percent of normothermic levels at 20° C in laboratory animals[12,13,26] and in humans.[32] These percent decreases in heart rate are surprisingly close to the percent reduction in total body oxygen consumption from normothermic levels.[11-13] Although the speed of myocardial contractions—that is, dP/dt or dT/dt (P = pressure, t = time and T = tension)—is decreased during hypothermia, the force of contraction is not depressed; thus there has been confusion about whether myocardial contractility is depressed during hypothermia.

The problem of cardiovascular collapse during hypothermia, then, is generally not a problem of myocardial

contraction, but of myocardial arrhythmias during deep hypothermia. Cardiac arrhythmias increase in severity as the body temperature falls below 28° C. The electrocardiogram shows a prolongation of the PR interval, widening of the QRS complex and a prolongation of the QT interval. Elevation of the ST segment or the appearance of a wave[33] rising steeply from the S wave is pathognomonic of hypothermia and warns of the possible onset of ventricular fibrillation, but it is frequently absent. Arrhythmias are frequent at temperatures below 28° C and may take the form of a nodal rhythm, premature ventricular contractions, atrioventricular block or even ventricular fibrillation.[6,28,32,33,37,58]

The major cause of death of an accidental hypothermic victim or an induced hypothermic patient is ventricular fibrillation, leading to cardiac standstill, the cause of which has been the subject of extensive and innovative studies. Although the mechanism of ventricular fibrillation during hypothermia is still not clearly defined, the following factors have been implicated[28, 39-42]: myocardial hypoxia, electrophysiologic disturbance and autonomic nervous system imbalance. When oxygen supply does not meet the demand of the myocardium, ventricular fibrillation can be the ultimate outcome. This is expected regardless of the temperature of the myocardium. Reduction in coronary blood flow during hypothermia from coronary vasoconstriction[43] and increased viscosity of the blood[32,42] are likely factors contributing to myocardial hypoxia.

Acid-base disturbance occurs with increased frequency during hypothermia below 25° C, unless adequate ventilation is maintained. Extracellular sodium and potassium concentrations are decreased and the chloride level is increased.[29,30] These electrolyte effects are enhanced by acid-base imbalance. That infusion of glucose results in greater myocardial uptake of potassium[29,30] and a lower incidence of ventricular fibrillation suggests a reduction in cellular potassium during hypothermia, which predisposes to ventricular irritability and fibrillation. Myocardial rhythmicity and contractility are significantly influenced by sympathetic and parasympathetic control. Anesthetics have a profound influence on the heart during induced hypothermia. Cyclopropane and pentobarbital are associated with a high incidence of ventricular arrhythmias, whereas ether and thiopental have the lowest incidence of ventricular arrhythmias in experimental animals and in humans.[32,44-49] Reduction of sympathetic activity tends to protect against hypothermic cardiac arrhythmias. That ether maintains a normal sinus rhythm, even at deep hypothermic levels, in dogs and in cardiac surgical infants suggests two important mechanisms for minimizing cardiac arrhythmias during hypothermia[44-49]: the maintenance of the sinoatrial node as the principal pacemaker and the suppression of ventricular irritability and ectopic foci.

Blood

Hypothermia causes a rise in hematocrit and an increase in viscosity with leukopenia and thrombocytopenia.[50,51] A temporary loss of plasma from the circulating volume either as a result of trapping in small peripheral vessels or an actual shift of water to the tissues is a contributing factor.[51,52] Leukopenia and thrombocytopenia are the result of sequestration of these cells in the liver and spleen and possibly also in the intestine and bone marrow. Thus, prolonged bleeding and clotting times are evident at 20° C.[53,54] These changes may not occur at moderate hypothermic levels and are reversible when rewarming from deep to moderate hypothermia.[32,54]

Blood Gas

The use of arterial blood gas determinations as an aid to patient care is an expected standard of medical practice today. Whereas there is general agreement that the arterial pH and partial carbon dioxide pressure (P_{CO_2}) of humans at 37° C should be around 7.40 and 40 mm of mercury, respectively, their ideal values at hypothermic levels are not well established. The problem with trying to establish normality of blood gas values during hypothermia stems from the fact that proper ventilation during hypothermia has not been clearly defined. Over two decades ago, Severinghaus[55] had suggested that "normal ventilation is that in which CO_2 elimination equals its rate of metabolic production as cooling progresses." From a metabolic standpoint, this definition must be correct, but how to interpret the blood gas value at hypothermic levels has posed problems, which have been the subject of recently published articles.[56-59]

A blood gas is generally measured at 37° C, the temperature of the electrodes. It has been customary, then, to correct the values to the patient's body temperature at which the blood was drawn. This generally accepted practice is based on the assumption that the ideal blood gas values at 37° C should be the physiologic standard with which hypothermic levels should be compared. However, a blood gas determined at 37° C with values of partial oxygen pressure (P_{O_2}) 120 and P_{CO_2} 40 mm of mercury and pH 7.4 will have corrected values of 84 and 32 mm of mercury and a pH of 7.48 at 32° C and 59 and 25 mm of mercury and a pH of 7.55 at 27° C by the Severinghaus corrections.[60] The question is whether these values represent hypoxemia and alkalosis during progressive hypothermia.

Rahn and co-workers[59] have suggested that the ideal state for the intermediary metabolism of cells is that of neutrality, because maximal cellular retention of ionized biosynthetic metabolites should occur at pH = pOH (the concentration of hydroxide ions). To defend cellular neutrality and to eliminate acid metabolites and carbon dioxide from the cell, an extracellular alkaline environment is provided by a compliant protein buffer, imidazole of histidine. Thus, at pH 7.4 the blood maintains a ratio of hydroxide ion (OH^-) to hydrogen ion (H^+) of 20:1 and a cellular pH of 6.8 where the OH^- to H^+ ratio is 1:1. This pH gradient between cells and blood of 35 vertebrates was maintained between 0° C to 40° C in vivo, while the bicarbonate content in each species was essentially constant with the

change in temperatures.[61] A constant bicarbonate content gives rise to a constant total blood carbon dioxide content. During hypothermia the reduction in oxygen consumption also results in a reduction in carbon dioxide production; the solubility of carbon dioxide in blood is increased, however. Therefore, alkalosis and hypocarbia during hypothermia are defended by physiologic mechanisms and physical behavior of gases. The use of the uncorrected values of pH and therefore P_{CO_2} in managing a hypothermic patient has thus been advocated.[56-59]

The addition of carbon dioxide during clinical hypothermia and extracorporeal circulation is based on the concern for cerebral perfusion associated with hypocarbia. The concern for cerebral hypoxemia may not be warranted since most laboratory studies have suggested that cerebral metabolism remains aerobic while the reduction in total body oxygen consumption is proportional to the reduction in cardiac output. In fact, maintaining a constant pulmonary ventilation during hypothermia and "respiratory alkalosis" results in better myocardial function in animals[12,13,26,62] and in humans.[32,44] This author also agrees with the clinical practice of not correcting the blood gas values read at 37° C to the temperature of the patient. Acceptable blood gas values measured at 37° C, the temperature of the electrode, require no alteration of mechanical ventilation or inspired carbon dioxide and oxygen concentrations.

Pharmacology

Since it is known that hypothermia depresses organ functions physiologically and biochemically, it is not surprising that all drug responses are exaggerated during hypothermia. Anesthetic requirements for inhalational anesthetics are uniformly decreased during moderate hypothermia.[63] Barbiturate toxicity is not only exaggerated by hypothermia, but hypothermia is reciprocally enhanced by barbiturate depression of thermoregulatory centers of the brain.[64] Phenothiazines by virtue of their α-adrenergic blocking action, in addition to their influence on the thermoregulatory centers, can also potentiate hypothermia.[65] The heart becomes increasingly sensitive to potassium-induced arrest and to calcium-induced fibrillation.[66] The requirement for a cardiotonic dose of digitalis glycosides is generally reduced,[67,68] but the cardiotoxic dose is increased.[69] The myocardium is also more tolerant of the cardiac depressant effects of morphine.[70] In general the cardiac stimulating effects of catecholamines and ketamine are enhanced during mild to moderate hypothermia and depressed at deep hypothermia.[71]

The termination of a drug response is usually the result of metabolism or excretion, or both. Both functions are progressively depressed during hypothermia. It is reasonable, then, to predict that all drugs tend to exert exaggerated responses during progressive hypothermia. The exception is the heart where the contractile process tends to be more resistant to depression during mild to moderate hypothermia.

Accidental Hypothermia

Unintentional exposure to cold from weather[72,73] or to the elements of an operating room is not uncommon. Operating room personnel are well aware of the rapidity by which anesthetized infants or burned patients can lose body heat if appropriate measures are not taken. Despite all precautions, it is at times impossible to maintain normothermia in patients with an open abdomen requiring transfusion of large amounts of fluid and blood. Acidosis and vasoconstriction as a consequence must be judiciously treated to ensure cardiovascular stability during the immediate postoperative period. In general, mild hypothermia can be effectively treated by surface rewarming and heated inspired gases and intravenously given fluids.

When there is moderate to deep hypothermia, particular attention should be given to cardiopulmonary support. Arterial catheterization for continuous pressure monitoring and blood gas determinations is indispensable. A pulmonary arterial catheter may be helpful, especially when cardiac output can be followed by a thermodilution technique. However, the risk of cardiac arrhythmias from introducing the catheter may be significant,[74] especially in an already vulnerable hypothermic heart. Bladder catheterization is important to monitor urinary output, which may also reflect adequacy of intravascular volume and organ perfusion. Of course, the core temperature must be continuously monitored.

Surface rewarming following moderate or deep hypothermia may worsen an already precarious clinical situation. Sequestrated cold fluids may be released from the peripheral vascular beds into the core bloodstream that will prolong the temperature gradient between the core and the periphery. Dilation of the peripheral vascular bed may induce hypotension and cardiac depression from the influx of cold fluid and acid metabolites released from these beds to the heart.[22] A hypothermic heart may not be able to respond to metabolic demands of the warm peripheral tissues. If surface rewarming is instituted for these patients, care must be exercised to not rewarm the patient too quickly, based on arterial blood gas values and cardiovascular stability. Extracorporeal rewarming may be necessary for deeply hypothermic victims.

Consciousness is usually lost at temperatures below 30° C. The use of corticosteroids has been advocated to prevent cerebral edema in an unconscious hypothermic patient.[22,32,73] Erythrocyte agglutination and sludging are associated with increased blood viscosity and deep hypothermia. Dextran 40 is useful for treating such patients during accidental or clinical hypothermia.[22,32] Rarely, an ominous, acute hemorrhagic pancreatitis may develop following prolonged hypothermia with subsequent rewarming.[22]

Finally, it is easy to be too zealous with the treatment of a hypothermic patient. One must always bear in mind when treating such patients that normothermia is not the standard on which to compare. A heart rate of 50 beats a minute with a mean arterial pressure of 60

mm of mercury may be quite adequate for a patient at 27° C.

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Medical Staff Conference

Cholestasis

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs David W. Martin, Jr, Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR SMITH:* *For many years the liver was considered to be the seat of human emotion, if not of the human soul. One has only to recall the terms "melancholia" or "choleric," or "feeling bilious." Or, one might even say that "splenetic" is an upstream hepatic emotion. Science has moved on, and most of us no longer give the liver that central focus in human affairs. But there is an important element of our faculty that still believes that to be true, and we will hear from one of them in this conference. The topic is cholestasis, and Dr Bruce Scharschmidt will discuss that entity.*

DR SCHARSCHMIDT:† Thank you, Dr Smith; it is gratifying to have the visceral organs put in their proper perspective.

Given a patient with cholestasis the most important task facing the clinician is to distinguish biliary obstruction from hepatocellular disease. This distinction is important because biliary obstruction usually requires active intervention, whereas we can generally do little about intrahepatic cholestasis except watch and wait. At least partially for this reason, intrahepatic cholestasis is often viewed as a "black box." We know that certain diseases and drugs are capable of causing it but we usually pay little attention to the cellular mechanisms involved. In the first half of this discussion, I should like to explore this black box. After reviewing pertinent background information regarding the anatomy and cellular physiology of bile secretion, I shall summarize current concepts regarding the pathophysiology of chlorpromazine- and estrogen-induced cholestasis. I shall then discuss selected features of cholestasis, specifically the possible reasons for the typical enzyme abnormalities that accompany cholestasis and the measurement and interpretation of serum bilirubin levels. Finally, I shall make several points regarding the use of various diagnostic techniques in the evaluation of cases of suspected extrahepatic obstruction.

Normal Bile Secretion

Anatomy

Figure 1 represents a schematic overview of bile formation.[1,2] Bile formation begins at the level of the *canaliculus,* much like urine formation begins at the glomerulus. However, unlike primary urine which is formed as the result of ultrafiltration, canalicular bile is formed as the result of active secretion by the hepatocyte of organic solutes such as bile acids and certain inorganic electrolytes. In the interdigestive state, canalicular bile is stored in the gallbladder where it is highly concentrated as the result of water and electrolyte reabsorption by the gallbladder mucosa. The larger bile ducts function as conduits and are also capable themselves of secretion and absorption of water and electrolytes. Most research in the field of bile formation has focused on events occurring at the level of the canaliculus because this is where bile secretion begins and where bile acids, bilirubin and lipids enter bile. Thus, an understanding of events occurring at the canalicular level is essential for an understanding of intrahepatic cholestasis. Figure 2 depicts anatomic relationships within the liver. Hepatocytes in the parenchyma are arranged in the form of single-cell-thick plates bathed on either side by sinusoidal blood. Bile is secreted into canaliculi, marked by arrows, which interconnect to form a chicken-wire-like network that ultimately empties into the interlobular bile ducts. Interlobular bile ducts are found in the portal tract, along with a portal venule and hepatic artery.

The microanatomy and environment of an individual hepatocyte is schematically shown in Figure 3. Again,

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ABBREVIATIONS USED IN TEXT

AMHPLC = alkaline methanolysis high pressure liquid chromatography
Na^+,K^+-ATPase = sodium-potassium-adenosine triphosphatase

one can appreciate that individual hepatocytes are joined together to form a single-cell-thick plate bathed on either side by sinusoidal blood. There are several aspects of this microanatomy that are particularly important to bile formation and therefore merit special attention. The sinusoidals are lined by endothelial cells with large *fenestrations* in their cytoplasms (Figure 3). These fenestrations are large enough to permit free access of molecules such as albumin and lipoproteins to the space of Disse, where they can come into direct contact with the hepatocyte plasma membrane. These fenestrations are thus important in understanding the liver's ability to export to the rest of the body large molecules such as albumin and lipoproteins, and they are also important in explaining the liver's nearly unique ability to extract from plasma tightly protein-bound substances such as bilirubin. That is, the uptake of tightly protein-bound substances by the liver appears to be facilitated by direct interaction between the hepatocyte plasma membrane and circulating albumin.

A variety of cellular structures are also important in bile formation. Microfilaments are contractile filamentous structures about 70 Å in diameter and are composed of polymerized actin. They are found throughout the cell, but tend to be concentrated around the canaliculus where they form a *pericanalicular microfilamentous web* (Figure 3, lower panel). Contraction of this pericanalicular web has actually been shown in hepatocytes in culture, and it is possible that phase-linked

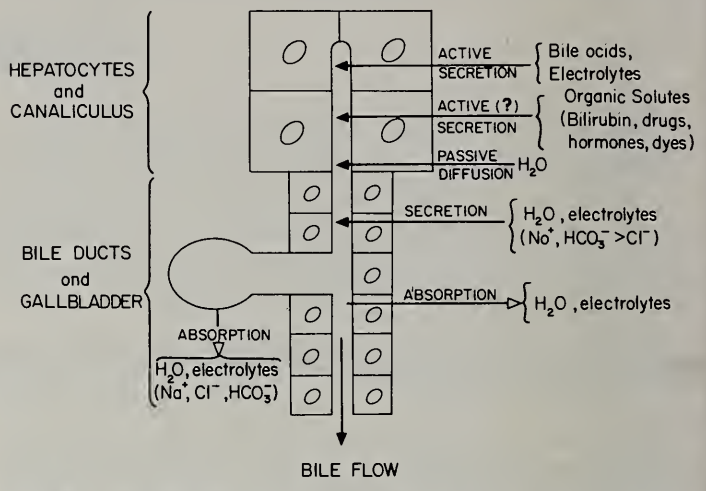

Figure 1.—Overview of bile secretion. Bile formation begins in the canaliculus with active transport of certain inorganic electrolytes and bile acids. Bilirubin, phospholipid and cholesterol also enter bile at the canaliculus. Canalicular bile is concentrated in the gallbladder and further modified in the bile ducts before entering the duodenum (reprinted with permission from Scharschmidt[1]).

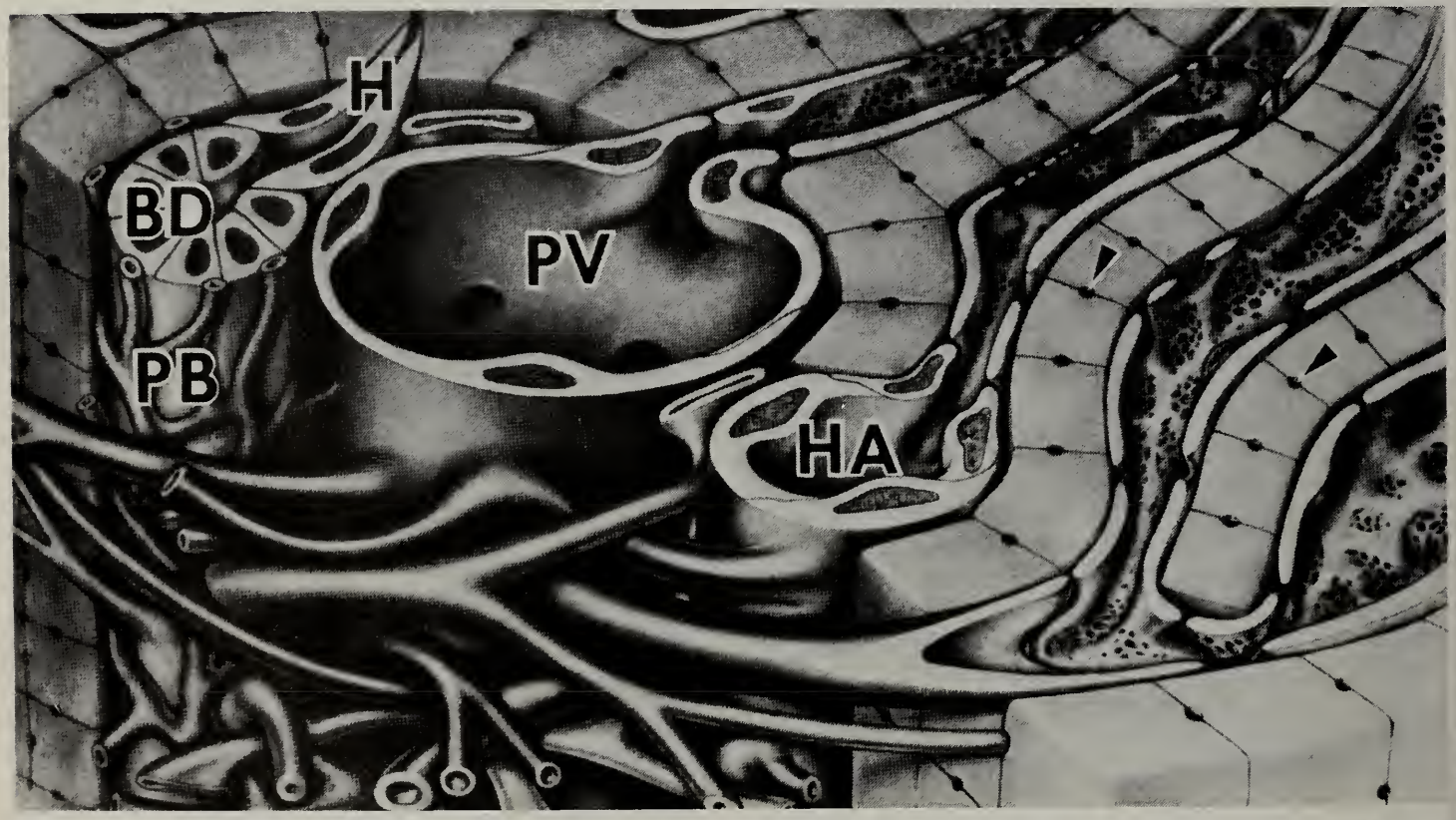

Figure 2.—Representation of anatomic relationship within the liver parenchyma. Bile is secreted initially into canaliculi **(arrows)** that run between hepatocytes in the liver cell plates and interconnect to form a chicken-wire-like network that empties into canals of Hering **(H)** and ultimately into interlobular bile ducts **(BD)** in the portal tract. The portal tract also contains branches of the portal vein **(PV)** and hepatic artery **(HA)**, from which the peribiliary vascular plexus **(PB)** originates (reprinted with permission from Jones et al[2]).

contractions may create a type of peristaltic motion that helps to "massage" the bile through the canalicular tree into larger collecting structures. Another structure important in bile formation is the *junctional complex*. As can be appreciated from Figure 3, bile formation in essence consists of movement of water and electrolytes from the blood into the canaliculus. The only anatomic barrier to free back diffusion of bile from the canaliculus into the space of Disse and the bloodstream is the junctional complex. The junctional complex has a number of components, including the belt desmosome and spot desmosomes, which seem to be important in cell-to-cell adhesion. Extending out from the spot desmosome are noncontractile tonofilaments that are believed to be important in maintaining cell structure in much the same way as guy wires in a circus tent are important in maintaining tent architecture. It is of interest that alcoholic hyaline or Mallory's bodies appear to represent an abnormal conglomeration of these tonofilaments. The *tight junction* is that component of the junctional complex that is primarily responsible for preventing free back diffusion of solutes from the canaliculus into the blood space. Viewed en face (Figure 3, lower panel), the tight junction appears to consist of closely spaced particles embedded in the cell membrane that form a series of anastomosing strands. These strands interdigitate with complementary strands on the adjacent cell so as to interlock like a zipper and "seal" the intercellular space. It appears that the integrity or "tightness" of the tight junction is related to the number and arrangement of the sealing strands that comprise it, and there is evidence to suggest that microfilaments play a role in maintaining the number and arrangement of the sealing strands.

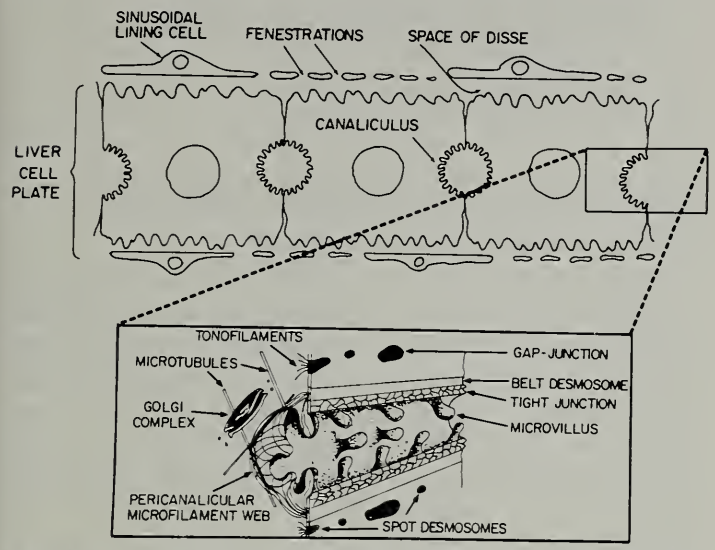

Figure 3.—A schematic of the bile secretory unit. The upper panel shows the anatomic arrangement of individual hepatocytes within the liver cell plate. The lower panel represents a blowup of the pericanalicular region of the hepatocyte, including the junctional complex and pericanalicular microfilament web (reprinted with permission from Scharschmidt[1]).

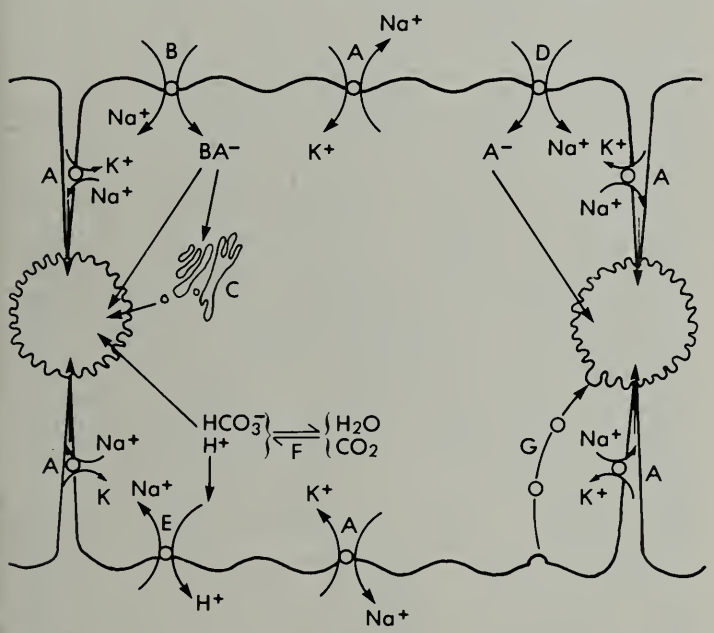

Figure 4.—A schematic of possible hepatocyte transport mechanism involved in canalicular bile secretion. Na^+,K^+-ATPase (A) on the sinusoidal and lateral aspects of the plasma membrane pumps sodium (Na^+) out of the cell, thereby creating an electrochemical gradient that provides the driving force for uptake of bile acids (BA^-) via sodium-coupled transport (B). Movement of bile acids to the canaliculus may involve membranous intracellular organelles such as the Golgi complex (C). Sodium-coupled uptake (D) of other anions (A^-) such as chloride has been proposed but not yet shown. Bicarbonate (HCO_3) transport may be driven by sodium and hydrogen ion (H^+) exchange (E) or a proton-translocating adenosine triphosphatase (not shown) in conjunction with carbonic anhydrase (F). Transport via a vesicular mechanism (G) is known to be responsible for secretion of immunoglobulin A and is postulated by some to play a role in bulk water movement and bile secretion (reprinted with permission from Scharschmidt[3]). CO_2 = carbon dioxide, H_2O = water.

Cellular Mechanisms of Bile Secretion

Current concepts regarding the cellular transport mechanisms involved in the formation of canalicular bile are depicted in Figure 4.[1-8] Canalicular bile formation is operationally divided into *bile acid-dependent flow,* that fraction directly related to the hepatic transport of bile acids, and *bile acid-independent flow,* that fraction apparently unrelated to bile acid transport which is believed to result from active secretion by the hepatocyte of inorganic electrolytes. Active bile acid transport and bile acid-dependent flow are dependent on sodium-potassium-adenosine triphosphatase (Na^+,K^+-ATPase). Na^+,K^+-ATPase is found in liver on the sinusoidal and lateral aspects of the plasma membrane. As in other cells, it pumps sodium out of and potassium into the hepatocyte. As a result of this pumping, Na^+,K^+-ATPase creates a steep electrical and chemical gradient tending to favor passive sodium entry into the cell. This electrochemical sodium gradient represents a source of potential energy much like the potential energy inherent in the water behind a dam. Just as the latter can be converted into useful work in the form of hydroelectric power, so the hepatocyte converts the potential energy inherent in the electrochemical sodium gradient into useful work in the form of bile acid transport.[5,7,8] That is, sodium entry into the cell, which is energetically downhill with respect to its electrochemical gradient, is

coupled to the inward movement of bile acids, which are thereby accumulated within the hepatocyte.

The subsequent movement of bile acids out of the hepatocyte into the canaliculus, which is energetically "downhill" with respect to their electrochemical gradient, is believed to create the driving force for bile acid-dependent bile flow. It is also important to point out that the sodium-coupled bile acid uptake mechanism and Na^+,K^+-ATPase are both integral components of the hepatocyte plasma membrane, and changes in the composition or physical properties of the membrane can affect their function.[4] All biologic membranes, including the hepatocyte plasma membrane, have as their core a phospholipid bilayer. The phospholipid head groups are oriented toward the exterior of the bilayer, and the phospholipid fatty acid tails are oriented toward the interior of the bilayer. The plasma membrane also contains cholesterol and integral membrane proteins, such as the putative sodium-coupled bile acid carrier and Na^+,K^+-ATPase. The phospholipid fatty acid tails in the interior of the membrane are not frozen in place but undergo random motion referred to as *membrane lipid fluidity*. In fact, lipid fluidity is measured by quantitating the rate of motion of probe molecules placed inside the plasma membrane. The important point from the aspect of bile formation is that changes in the composition or physical properties of the hepatocyte membrane appear to affect the function of the bile acid carrier, Na^+,K^+-ATPase, and, by implication, a number of other carrier systems presumably important in bile formation.

The cellular mechanisms involved in bile acid-independent bile formation are less clear than those for bile acid-dependent bile formation. Although it has generally been held that N^+,K^+-ATPase plays a central role, this concept has received little direct experimental support. It was postulated that bile acid-independent bile formation might result from sodium-coupled chloride transport, a mechanism conceptually analogous to sodium-coupled bile acid transport and believed to be important in other epithelia such as gallbladder. However, experimental studies suggest that this is not the case.[6] Indeed, bile acid-independent bile formation appears to be largely dissociable from any specific requirement for either sodium or Na^+,K^+-ATPase.[4,7] In contrast, bicarbonate secretion does appear to be important in bile acid-independent bile formation and,[7] as shown in Figure 4, it is presumably attributable to active proton transport as a result of either sodium and hydrogen ion exchange or a plasma membrane-associated proton translocating adenosine triphosphatase (or both). Whatever the precise mechanism(s) involved, it also seems to be affected by changes in the composition or physical properties of the surrounding membrane lipids. With this brief glimpse into the cellular mechanisms important for normal bile formation, it is worthwhile looking at certain forms of intrahepatic cholestasis.

TABLE 1.—*Hepatic Effects of Chlorpromazine and Chlorpromazine Metabolites*

Forms insoluble complexes with bile acids
Alters liver plasma membrane lipid fluidity
Alters electron-microscopic appearance of hepatocyte membranes
Alters activity of membrane-associated enzymes
Alters polymerization of actin

Pathophysiology of Intrahepatic Cholestasis

Chlorpromazine-Induced Cholestasis

Chlorpromazine is a drug that is rather notorious for its propensity to cause cholestasis. Overt cholestatic hepatitis develops in up to 1 percent of patients given this drug and asymptomatic alkaline phosphatase elevation occurs in up to 50 percent of patients. Most patients recover within four to eight weeks after they stop taking the drug, but a small proportion of patients have cholestasis that persists for months after the drug is withdrawn.

Administration of chlorpromazine to nonhuman primates or rodents promptly causes cholestasis, and current information regarding the effects of chlorpromazine and certain of its active metabolites on the hepatocyte are summarized in Table 1.[9-13] Chlorpromazine is a cationic detergent that can form insoluble precipitates with anionic bile acids. It can also bind reversibly with hepatocyte plasma membranes and can alter their physical properties, including lipid fluidity. In conjunction with this, there is a striking change in the electron-microscopic appearance of liver plasma membranes. Probably as the result of interaction between drug and membrane and changes in lipid fluidity, there is inhibition of membrane-associated enzymes such as Na^+,K^+-ATPase. Finally, chlorpromazine and certain metabolites alter the in vitro polymerization of actin to form microfilaments. Assuming that this also occurs in vivo, impaired microfilament function might contribute to chlorpromazine-induced cholestasis by impairing canalicular contractility or by altering the integrity of the tight junction, or both.[14,15] Chlorpromazine has also been shown to interfere with the function of calmodulin in many cell types. Given the importance of calcium and calmodulin in regulation of a variety of cellular functions, this observation may have potentially important implications with respect to the effect of chlorpromazine on bile formation. The overriding message here is that chlorpromazine affects a number of cellular functions and structures believed to be important in bile formation, and it is very tempting to speculate that these effects help account for the propensity of this drug to cause cholestasis.

Estrogen-Induced Cholestasis

In addition to cholestasis induced by drugs, increasing knowledge is emerging regarding certain endogenous forms of cholestasis.[4,16-18] The best such example is cholestasis related to estrogens, which typically occurs either during pregnancy or following the administration

of estrogens in the form of oral contraceptives. Intrahepatic cholestasis of pregnancy is relatively rare in the United States but is quite frequent in certain other countries. In Chile, for example, it complicates nearly one in ten pregnancies. Family studies have made it clear that there is a genetic predisposition to this disorder, though the underlying mechanism for such predisposition is unknown. It typically occurs in the third trimester of pregnancy, though the time of onset varies. Laboratory studies typically reveal disproportionate elevation of the serum alkaline phosphatase level, though a modest rise in aminotransferase (transaminase) is not uncommon. A liver biopsy specimen usually shows nonspecific cholestasis with minimal hepatocellular necrosis, and the disorder usually resolves rapidly after delivery. It has a tendency to recur in later pregnancies, though the severity and time of onset can vary considerably from pregnancy to pregnancy. It typically recurs following the administration of estrogens in the form of birth control pills.

Studies completed during the past several years have provided potentially important insights into the cellular mechanisms that may be responsible for estrogen-induced cholestasis, and they are best seen in the context of the cellular mechanisms of bile secretion depicted in Figure 4.[4,16-18] Estrogens cause rather striking changes in both hepatic cholesterol metabolism and cellular structures. These changes include apparent alterations in the activity of enzymes that are responsible for conversion of cholesterol to bile acids and for the formation of cholesterol esters; increased cholesterol content of bile, which helps explain why women have a higher incidence of cholesterol gallstones than do men; increase in the cholesterol content of hepatocyte plasma membranes; decreased membrane lipid fluidity; decreased activity of certain membrane-associated enzymes such as Na^+,K^+-ATPase, and an apparent increase in tight junction permeability so as to facilitate the back diffusion of molecules from the bile to the blood. It is likely that the alterations in the activity of membrane-associated enzymes, lipid fluidity, junctional permeability and bile secretory functions are a result of the primary alteration in plasma membrane lipid composition. Thus, just as with chlorpromazine, it appears that changes in the plasma membrane play a central role in the pathophysiology of cholestasis. Additional evidence that these membrane changes are causally related to cholestasis is provided by the observation that certain nonionic detergents, which can reverse these changes in lipid fluidity when mixed with isolated plasma membranes in vitro, can also reverse estrogen-induced cholestasis when administered to intact animals.

With this evolving understanding of the cellular mechanisms involved in cholestasis, it may not be too unthinkable to postulate that forms of treatment for specific types of intrahepatic cholestasis will ultimately prove feasible. In this regard, it is interesting to review a series of studies carried out with a compound called *S*-adenosylmethionine.[19] *S*-adenosylmethionine is an endogenous compound that participates as the methyl donor in a variety of methylation reactions. In experimental animals, *S*-adenosylmethionine has been shown to reverse the tendency of estrogens to produce both cholestasis and cholesterol supersaturation of bile. Experimental work has recently been extended to humans, and *S*-adenosylmethionine was again shown to reverse the estrogen-induced cholesterol supersaturation of bile. A preliminary report suggests that *S*-adenosylmethionine may have beneficial effects when administered to women with cholestasis of pregnancy. Exactly how this compound works is not clear, but there are at least two possibilities. First, it may alter estrogen metabolism. *S*-adenosylmethionine is a methyl donor and has been shown to enhance the biliary excretion of methylated estrogen metabolites. Second, *S*-adenosylmethionine participates in reactions in which membrane phospholipids are methylated in situ so as to alter lipid fluidity. Thus, *S*-adenosylmethionine may block estrogen effects either by enhancing their metabolism or directly antagonizing their effects at the membrane level. Of course, these studies are preliminary and we are a long way from using an experimental compound such as *S*-adenosylmethionine to treat a basically benign disorder such as cholestasis of pregnancy. However, these studies are noteworthy in that they show how more information regarding the pathophysiology of intrahepatic cholestasis may be turned to therapeutic advantage.

Features of Cholestasis

Abnormal Serum Enzymes

I would like to turn your attention now to selected features of cholestasis, starting first with the abnormal serum enzymes. Why is it that in patients who have cholestasis a disproportionate rise in the level of the alkaline phosphatase relative to aminotransferases tends to occur? (There are exceptions to this generalization. For example, patients who pass a common duct stone can occasionally have striking, albeit usually transient, elevation of their aminotransferases.) In understanding the reason for the typical pattern in enzyme elevation, it is first helpful to point out that these enzymes differ in their intracellular location. Alkaline phosphatase, 5′-nucleotidase and leucine aminopeptidase are located at least in part in the hepatocyte plasma membrane. In contrast, aminotransferases are found in the cytoplasm and in intracellular organelles. With this in mind, the sequence of events following, for example, the lodging of a stone in the common duct may be as follows.[20-23] First, there is elevation in the concentration of bile acids not only in serum, but also in and around the hepatocytes. Bile acids, which are potent physiologic detergents, then solubilize or release these plasma membrane-associated enzymes into the circulation. In conjunction with more release, there is quite clearly more enzyme synthesis. This greater synthesis may reflect a reparative effort of the hepatocyte, or it may be a direct effect of bile acids. The net effect of the increased release and greater synthesis is a rise in the alkaline phosphatase level in serum. Thus, the greater release of

alkaline phosphatase and other enzymes such as 5′-nucleotidase would reflect the ability of bile acids to solubilize selectively plasma membrane enzymes without grossly disrupting the plasma membrane so that loss of intracellular aminotransferases occurs. There is circumstantial evidence to support this hypothesis. It has, for example, been shown that bile acids are capable of altering the physical properties of plasma membranes in vitro,[20] and bile acids have been used for decades by biochemists to solubilize membrane-associated enzymes. Even more compelling is the observation that in some patients with extrahepatic cholestasis, alkaline phosphatase in the bloodstream may be found in association with phospholipid vesicles. These vesicles contain other plasma membrane-associated enzymes such as 5′-nucleotidase and, in fact, may represent circulating fragments of the hepatocyte plasma membrane.[23]

Hyperbilirubinemia

I will now add a few words about hyperbilirubinemia, specifically how it is measured and how to interpret it. The conventional technique for measuring bilirubin involves a reaction of serum with an aromatic diazonium salt (diazo reagent) to produce a blue color that is quantitated spectrophotometrically. As shown below, the color generated in the absence of an "accelerator" such as methanol results in what is called the direct-reacting fraction, which is generally considered equivalent to conjugated bilirubin.

$$\text{serum} \xrightarrow[\text{(no accelerator)}]{\text{diazo reagent}} \text{direct-reacting fraction (conjugated bilirubin)}$$

$$\text{serum} \xrightarrow[\text{(with accelerator)}]{\text{diazo reagent}} \text{total bilirubin}$$

The reaction of serum with diazo reagent in the presence of an accelerator yields total bilirubin, and the difference between these two is called the indirect-reacting fraction, which is usually equated with unconjugated bilirubin. This technique has two very important shortcomings. First, the diazo reagent is relatively nonspecific; that is, it reacts with substances other than bilirubin. This nonspecificity may explain, for example, the occasional spurious hyperbilirubinemia seen in patients receiving propranolol therapy, inasmuch as the diazo reagent appears to react with certain propranolol metabolites. Second, the direct- and indirect-reacting fractions are really quite inaccurate reflections of conjugated and unconjugated bilirubin, respectively.

Recently a newer, more specific technique has been developed for measuring bilirubin,[24] but to describe it I need to refresh your memory very briefly about the bilirubin molecule. Bilirubin is a tetrapyrrole and it exists in plasma in four forms: in unconjugated form, in which the two propionic acid groups on the inner pyrrole rings are free; in diconjugated form, in which both these propionic acid groups are joined in ester linkage to glucuronic acid or other sugars, or in one of two isomeric monoconjugated forms, in which one or the other propionic acid group is bound to glucuronic acid or another sugar. The newer technique, which I will call the AMHPLC assay, converts monoconjugated or diconjugated bilirubin, which is water-soluble, into hydrophobic methyl esters by alkaline methanolysis (AM) so that a methyl group rather than a sugar is bound to the propionate group. These hydrophobic methyl esters can then be separated and quantitated along with unconjugated bilirubin by high pressure liquid chromatography (HPLC). This AMHPLC technique has been applied clinically with some interesting findings.[24,25] The first finding to emerge was that conjugated bilirubin is essentially undetectable in normal serum and in the serum of patients with Gilbert's syndrome. Thus, the 0.2 to 0.4 mg per dl direct-reacting fraction frequently seen in the serum of healthy adults represents something other than conjugated bilirubin. The second point is that in patients with overt hepatobiliary disease, conjugates are nearly always present and in fact account for most of the circulating bilirubin (Figure 5).

As is illustrated in Figure 6, the circulating conjugates in patients with hepatobiliary disease are about equally distributed between diconjugates and the two

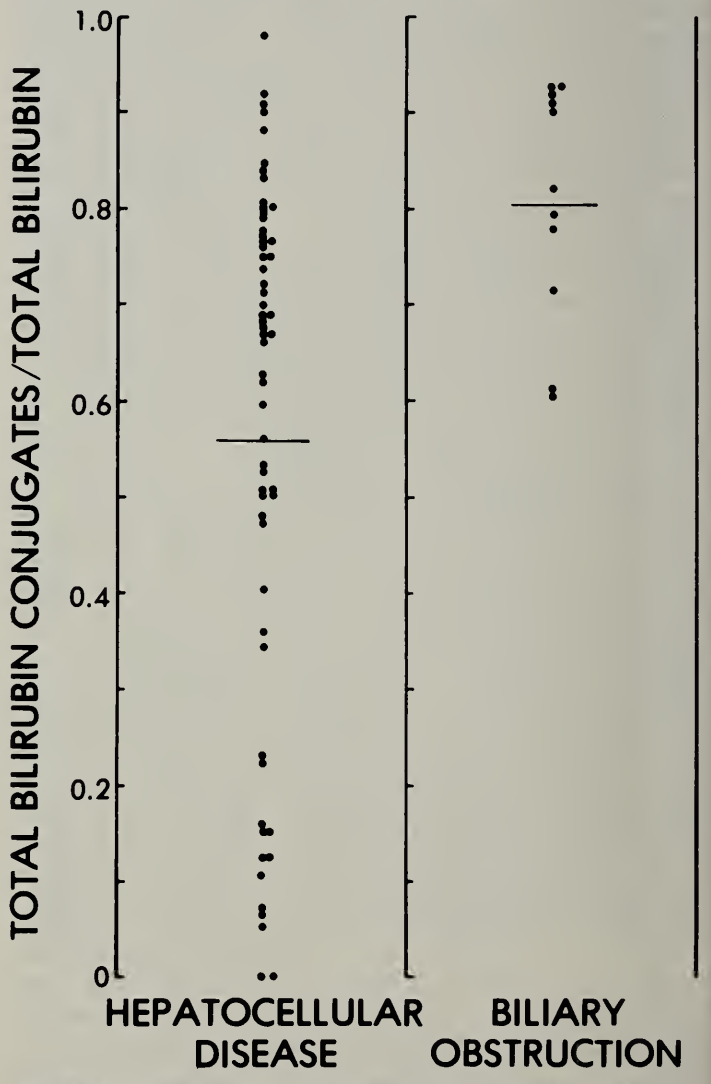

Figure 5.—The fraction of total bilirubin present as conjugates in 91 serum specimens from 65 patients with hepatobiliary disease (reprinted with permission from Scharschmidt et al[25]).

isomeric monoconjugated forms. The third point, shown in Figure 7, is that there is little or no relationship between the direct-reacting fraction as conventionally measured and the proportion of bilirubin conjugates. The fourth point is that compared with the AMHPLC assay, the conventional diazo assay erratically and occasionally greatly overestimates the concentration of total bilirubin in the serum of patients with hepatobiliary disease. Finally and unfortunately, as shown in Figure 5, even the AMHPLC assay is not likely to be useful in the differential diagnosis of jaundice, that is, in distinguishing hepatocellular disease from biliary obstruction. Whereas the proportion of conjugates is higher in patients with biliary obstruction than in patients with hepatocellular disease, the overlap between groups is so great that the test is of little help in an individual patient.

A recent preliminary report may help explain the discrepancy between the values for total bilirubin in patient sera obtained with the AMHPLC and conventional assays.[26,27] It appears that conjugated, but not unconjugated, bilirubin binds covalently with serum albumin to yield a complex that reacts with diazo reagent. Because serum proteins are denatured and precipitated in the AMHPLC but not the conventional assay, these diazo-positive pigments are detected only by the conventional assay. In addition to its obvious implications with respect to the interpretation of serum bilirubin measured by different techniques, the presence of conjugated bilirubin covalently bound to albumin and therefore not readily excreted may help explain the occasionally slow resolution of conjugated hyperbilirubinemia in patients recovering from acute liver injury.

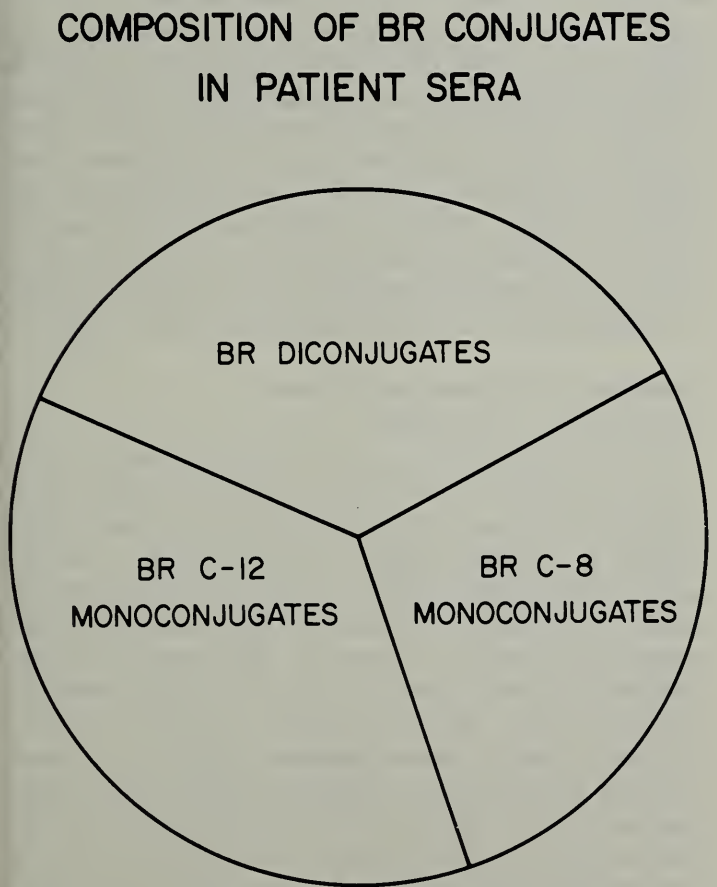

Figure 6.—Distribution of bilirubin conjugates in 91 serum specimens from 65 patients with hepatobiliary disease. Bilirubin diconjugates and bilirubin monoconjugates in which either the C-8 or C-12 propionic acid group was conjugated were about equally represented in patient sera. BR = bilirubin.

The conclusions to be drawn from this recent information derived from the use of the AMHPLC technique are summarized below and in Table 2. First, measurement of bilirubin by the conventional diazo assay in the presence and absence of an accelerator is a very poor way of measuring conjugated and unconjugated bilirubin. Second, conjugates are undetectable in normal serum and in the serum of patients with Gilbert's cholemia by the AMHPLC assay. As a corollary, the presence of detectable conjugates in serum will prob-

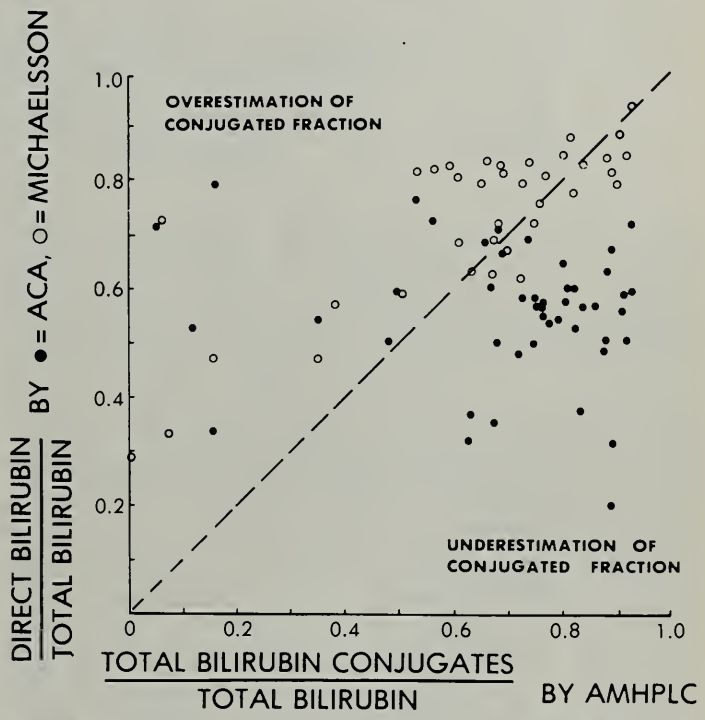

Figure 7.—Comparison of conventional diazo assays with the alkaline methanolysis-high pressure liquid chromatography (AMHPLC) techniques for measurement of conjugated bilirubin in serum. The ACA assay, an automated assay used in many hospital laboratories, and a manually performed reference assay (Michaelsson) showed little or no correlation with the AMHPLC assay as indicated by the very wide scatter of points around the theoretic line of identity (reprinted with permission from Scharschmidt et al[25]).

TABLE 2.—*Hyperbilirubinemia: Measurement and Interpretation*

The direct- and indirect-reacting fractions as measured by conventional diazo assays are inaccurate reflections of conjugated and unconjugated bilirubin
By newer and more specific assays, bilirubin conjugates are essentially undetectable in sera from healthy persons and those with Gilbert's syndrome but are present in the serum of most patients with overt hepatobiliary disease
The proportion of conjugates present in serum, unless zero, is of little value in differential diagnosis
Some conjugated bilirubin in serum may be covalently bound to albumin

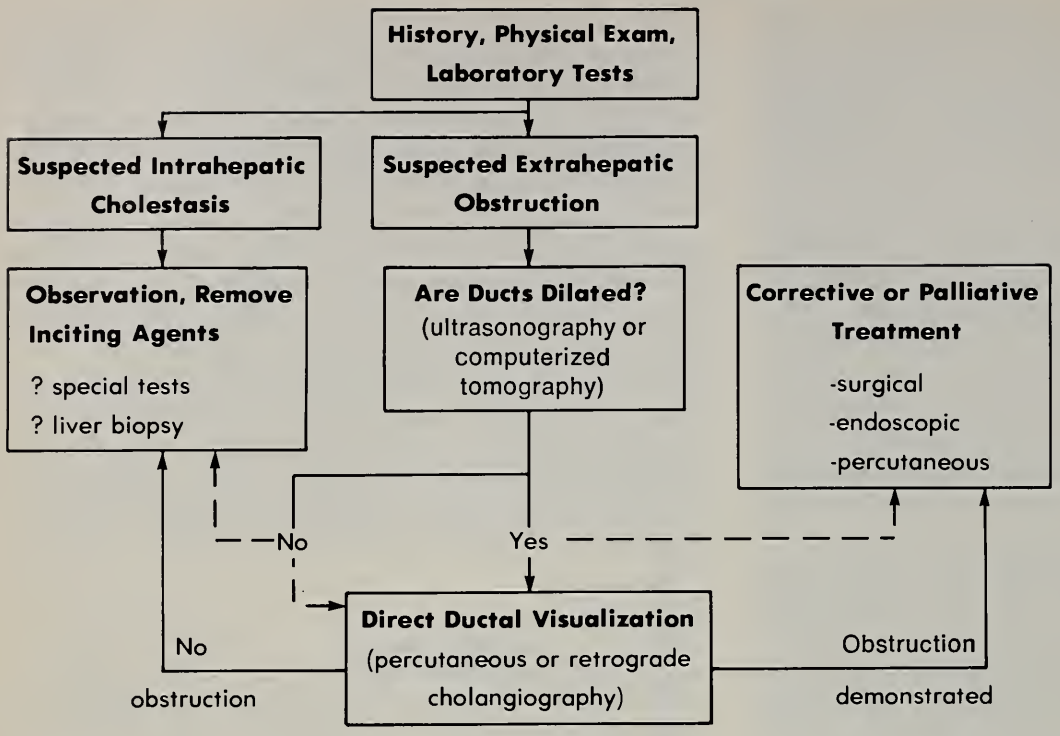

Figure 8.—Outline of the conventional clinical approach to a patient who has cholestasis (reprinted with permission from Scharschmidt[28]).

ably prove to be a relatively reliable indicator of hepatobiliary dysfunction. Indeed, it is precisely in this situation, that is, distinguishing Gilbert's disease from hepatobiliary disease in a patient with low level hyperbilirubinemia, that the AMHPLC assay is likely to be of greatest value. The third conclusion is one that was already known but has now been reinforced. With the exception of pure unconjugated hyperbilirubinemia suggestive of hemolysis or Gilbert's disease, fractionation of serum bilirubin is of little diagnostic value. To state it another way, once one knows that conjugates are present, it is not helpful in terms of a differential diagnosis to know whether they constitute 10 percent or 90 percent of total serum bilirubin. Finally, perhaps analogous to the binding of glucose to hemoglobin and other body proteins, it appears that conjugated bilirubin may bind covalently to serum albumin.

Clinical Approach to Suspected Biliary Disease

Overview

I should now like to make several points regarding the approach to a case of suspected extrahepatic obstruction. The evaluation of such a case has changed rather dramatically in the last several years with the advent of newer radiologic and endoscopic techniques. Figure 8 depicts the conventional approach to a patient who has cholestasis.[28] If, on the basis of history, physical examination and laboratory tests, there is reason to suspect extrahepatic obstruction, a conventional first step is to try by ultrasonography or computerized tomography to determine whether ductal dilatation is present. The presence of ductal dilatation is relatively specific for obstruction, and current medical literature suggests that 35 percent of patients with obstructive jaundice have ductal dilatation.[29-33] This apparently very high sensitivity will be discussed later.

If there is evidence of ductal dilatation, the usual next step is direct ductal visualization by percutaneous or retrograde cholangiography.[34-36] Percutaneous cholangiography successfully shows the biliary tree in about 90 percent of cases in which intrahepatic ducts are dilated. When intrahepatic ducts are not dilated its success rate is somewhat less. Endoscopic retrograde cholangiography successfully visualizes the bile ducts in about 85 percent of cases whether or not the ducts are dilated. The complication rate of both these procedures is between 5 percent and 10 percent. Both can cause cholangitis, particularly in a patient with obstruction. Percutaneous cholangiography can cause bleeding or bile leakage into the peritoneal cavity and retrograde cholangiography can occasionally cause pancreatitis.

Sensitivity of Ultrasonography and Computerized Tomography

While the general approach outlined in Figure 8 is widely accepted, there are a few important points worthy of emphasis. The first regards the relative sensitivity of ultrasonography and computerized tomography. Most published studies have dealt with jaundiced patients, and jaundice tends to imply relatively high-grade fixed obstruction. However, gallstones, which are probably the most common cause of biliary disease, very often cause only intermittent or partial obstruction. In this setting, ductal dilatation might be expected to be less frequent; in fact, the little available data suggest that up to 40 percent of patients with proved common duct stones and little or no hyperbilirubinemia fail to exhibit ductal dilatation by computerized tomography.[37] The sensitivity of these tests may also be compromised in other situations. For example, patients with cirrhosis frequently do not have dilatation of the intrahepatic ducts despite high-grade obstruction, a

finding probably attributable to the poor compliance of the scarred cirrhotic parenchyma. In addition, whereas ultrasonography is quite reliable in detecting gallbladder stones, it is surprisingly insensitive in detecting stones in the common duct. This probably reflects the lesser or absent fluid-calculus interface surrounding ductal stones as compared with gallbladder stones.

The major point to be made here is that whereas ultrasonography and computerized tomography are unquestionably of value in diagnosing ductal disease, they are by no means infallible. When there exists a strong clinical suggestion of obstruction, one should not be dissuaded from further investigation if these tests fail to show ductal pathology. Indeed, in certain circumstances it may be appropriate to proceed directly to percutaneous or retrograde cholangiography. For example, given a patient with biopsy-proved cirrhosis who previously had undergone a cholecystectomy for gallstones and who now presented with intermittent episodes of right upper quadrant pain, jaundice and fever, it would be reasonable to proceed to direct ductal visualization.

Other Tests

A variety of tests are no longer used in the routine diagnostic workup of patients with cholestasis and, in fact, are not even included in the algorithm in Figure 8. One of these is cholangiography using intravenously administered contrast medium and the reasons are as follows.[38,39] First, even when the bilirubin concentration is less than 3 mg per dl, the duct is adequately visualized in only about half the patients. Second, even when the duct is adequately seen, cholangiography fails to detect about a third of proved common duct stones. Third, although generally classified as a noninvasive technique, cholangiography is not without risk and is, in fact, associated with about a 1 percent incidence of hypersensitivity reactions characterized by hypotension or dyspnea.

Liver biopsy is another test that is no longer routinely useful in cases of suspected obstruction. The problem with liver biopsy is not that it is too dangerous in a patient with obstruction. In fact, the incidence of serious complications in patients with large duct obstruction is around 1 percent.[40] This is higher than the complication rate of liver biopsy overall, but not prohibitively high. Rather, the problems are, first, that liver biopsy is relatively insensitive in providing a diagnosis of obstruction. Most patients with early or partial obstruction tend to have only nonspecific or suggestive findings such as portal tract edema, canalicular bile plugs or ductular proliferation. Diagnostic findings such as bile infarcts, bile lakes and bile plugs in the interlobular ducts tend to occur in patients with prolonged or high-grade obstruction in whom the diagnosis is clinically apparent. The second problem is that even when findings diagnostic of extrahepatic obstruction are present, liver biopsy typically provides no information regarding the nature or site of the obstruction.

Diagnosis of Gallbladder Stones

Cholecystography using orally given contrast medium has been for many years the standard procedure for making the diagnosis of nonobstructing gallbladder stones. However, its position has recently been challenged by several studies that have compared real-time ultrasonography with cholecystography.[41,42] Both tests appear to be relatively specific when positive. The difference has been in sensitivity. It appears that about 10 percent of gallstones may be missed by cholecystography. In contrast only about 5 percent of stones appear to be missed by real-time ultrasonography, and stones missed by cholecystography are frequently detected by ultrasonography.[43] Because of this possibly higher sensitivity, because it does not involve radiation exposure and because it provides an immediate answer, some proponents have suggested that ultrasonography should replace cholecystography. However, ultrasonography more than cholecystography critically depends on the skill and experience of a radiologist. Thus, the very impressive figures for the sensitivity and specificity of ultrasound procedures noted above may not be representative of the community at large. I think that cholecystography remains a perfectly acceptable first procedure for the routine outpatient work-up for suspected gallstones. In contrast, ultrasonography has obvious advantages in the case of a pregnant patient wherein radiation needs to be avoided or in an acutely ill patient when one needs an answer in a hurry.

The final point that I shall make regards the newer biliary radionuclide scanning agents, including HIDA (Lidofenin), IDA and PIPIDA (Iprofenin) technetium Tc 99m. These agents are all substituted iminodiacetic acids. They are taken up by hepatocytes and excreted in bile, so that under normal circumstances they visualize the biliary tree and the gallbladder. Failure of the gallbladder to visualize in a patient who has not previously had it surgically removed is taken as evidence of cystic duct obstruction and, by implication, acute cholecystitis. Published data suggest that this test exhibits greater than 90 percent sensitivity and specificity in making this diagnosis,[44] but these figures may prove to be a little high. With respect to sensitivity, it is worth mentioning that this test does miss some cases of acalculous cholecystitis in which there is no cystic duct obstruction. With respect to specificity, it is important to point out that it is frequently positive in patients with chronic cholecystitis. Thus, it may not be specific for acute cholecystitis per se but rather for gallbladder disease in general. There is little doubt, however, that it is better than cholangiography (intravenous) for making the diagnosis of acute cholecystitis. Finally, this test has recently been suggested to be of value in making the distinction between hepatocellular disease and biliary obstruction, and in the best studies it has been reported to make the distinction correctly nine out of ten times.[44-46] Again, several caveats bear mention. First, its discriminatory ability falls off rapidly as the bilirubin concentration exceeds 10 mg per dl. Second, those radiologists who have found the test to be

most reliable in differential diagnosis have used the strictest criteria for interpretation and have found that about 30 percent to 40 percent of their studies are inconclusive. Finally, the resolution of this technique is relatively poor and it is unlikely to replace direct cholangiography as a means of localizing or characterizing biliary tract obstruction.

Summary

I have covered selected and what I think are interesting aspects of the pathophysiology and diagnosis of cholestasis. Given the broad nature of the topic, some important issues have gone undiscussed and for those I refer readers to one of several recent reviews.[1,3,28,47,48]

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Epitomes

Important Advances in Clinical Medicine

General Surgery

The Scientific Board of the California Medical Association presents the following inventory of items of progress in general surgery. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers or scholars to stay abreast of these items of progress in general surgery that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on General Surgery of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Primary Hyperparathyroidism

PRIMARY HYPERPARATHYROIDISM occurs in 1 of every 700 persons. There are three questions concerning patients with primary hyperparathyroidism: Should parathyroidectomy be recommended for patients with asymptomatic hyperparathyroidism? Is there such a condition as normocalcemic hyperparathyroidism and how is it best diagnosed? How many parathyroid glands should be removed at operation?

In about 25 percent of patients with minimal or asymptomatic hyperparathyroidism, complications from this disease will develop in ten years; moreover, it is impossible to predict in which of the patients these problems will develop. Metabolic studies show that asymptomatic patients receive the same metabolic benefits from successful parathyroidectomy as symptomatic patients, such as decreased urinary calcium excretion, increased bone density and improved creatinine clearance. Also, once some of the conditions associated with chronic hyperparathyroidism, such as renal dysfunction and hypertension, are established, they may worsen despite successful parathyroidectomy. Thus, if the diagnosis is certain and there is no contraindication to operation, parathyroidectomy is recommended.

Another important question is whether a normocalcemic patient with renal stones has normocalcemic hyperparathyroidism or idiopathic hypercalciuria. At least three serum calcium levels and a serum parathyroid hormone level should be determined in these patients. If there is a simultaneous increase in both calcium and parathyroid hormone, then the patient has hyperparathyroidism (primary or ectopic). If the parathyroid hormone level is low and serum calcium level normal, then the patient has hypercalciuria. The increased urinary calcium concentration in these patients with idiopathic hypercalciuria is due to increased calcium absorption from the gastrointestinal tract, probably due to defective vitamin D metabolism. If the serum parathyroid hormone level is raised and the serum calcium level is normal then the patient has either idiopathic hypercalciuria due to an increased loss of calcium in the urine or normocalcemic hyperparathyroidism. The latter two disorders can be differentiated by treating a patient with thiazide diuretics. These diuretics decrease urinary calcium excretion and thus the parathyroid hormone level will decrease in patients with idiopathic hypercalciuria because renal calcium loss is corrected. In patients with normocalcemic hyperparathyroidism the serum calcium level will usually increase and the parathyroid hormone level will not decrease. Because thiazide diuretics are recommended for patients who have nephrolithiasis, this treatment is both diagnostically and therapeutically effective.

During the past ten years there has been some controversy concerning how much parathyroid tissue should be removed in patients with primary hyperparathyroidism. Virtually all surgeons today recommend identification of four parathyroid glands and removal of only the enlarged gland when only one is abnormal. Biopsy of other glands is optional. Subtotal parathyroidectomy is advised for patients with primary and secondary parathyroid hyperplasia. Prophylactic subtotal parathyroid-

ectomy for patients with adenomatous parathyroids is to be discouraged except perhaps in patients with familial hyperparathyroidism or multiple endocrine adenomatosis.

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Cutaneous Melanoma

MELANOMA ORIGINATING in the skin is the most serious of cutaneous malignant diseases. The incidence is increasing in the white race, but fortunately so is the cure rate due to treatment at an earlier stage of disease. Genetic factors, possibly actinic radiation and some chemicals are among the possible causes. Melanoma develops from melanocytes at the site of a preexisting mole in 50 percent to 75 percent of cases. Trauma with infection tends to bring the lesion to the attention of the patient. Prevention focuses on screening out ultraviolet irradiation and removing suspicious moles.

Histopathologists have differentiated three main types of cutaneous melanoma: lentigo maligna, superficial spreading melanoma and nodular melanoma. The third type carries the worst prognosis, especially when ulcerated. Other more rare subtypes include melanoma arising in a giant hairy nevus or a blue nevus and in the volar-subungual region (acral lentiginous melanoma).

Two methods of microstaging have become widely used and valuable in estimating prognosis. With the availability of the methods of staging, treatment modifications have been developed that allow for less radical treatment in early stages and a more rational use of radical surgical treatment in more advanced stages.

Clark (1969) proposed a microstaging system that depends on the level of invasion. Level I invasion involves epidermis alone, progressing to level V, in which tumor penetrates all layers of dermis to involve underlying subcutaneous tissue. Breslow (1970 and 1975) microstaged melanoma by measuring the maximal tumor thickness.

The most accurate prognostic information is obtained by first measuring tumor thickness, then the level of invasion. This technique is widely used to guide the extent of treatment to the primary tumor and regional nodes.

In clinical stage I (tumor confined to primary site), these two measurements plus location have allowed division of cases of melanoma into three risk categories for the primary tumor (that is, low, intermediate and high risk). Using these same categories one can estimate the chances of occult regional metastasis and select those patients whose prognosis might be improved by regional node dissection.

All patients with enlarged suspicious regional nodes in the absence of distant metastasis should have radical regional node dissection. The development of local recurrence and satellitosis on an extremity is best managed by hyperthermic regional perfusion with chemotherapeutic agents to control local disease and avoid amputation. Major amputation is occasionally still indicated and may prolong survival. When distant metastasis occurs such as to the lung, surgical removal of the metastatic lesion for diagnosis may result in cure.

Administration of presently available chemotherapeutic agents, singly or in combination, leads to a partial response in only a small percentage of patients (about 20 percent).

Immunotherapy alone or combined with chemotherapy may be useful as an adjuvant therapy in treating high-risk melanoma patients. More effective chemotherapeutic drugs and further advances in immunology and immunotherapy will be needed before results can be improved in disseminated melanoma.

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Stapling Instruments in General Surgery

ALMOST 75 years have passed since the first stapling instrument to be used in general surgery was introduced in 1908 in Budapest by the combined efforts of Victor Fischer, a surgical instrument designer, and Humer Hultl, a prominent surgeon of that Hungarian city. Aladar von Petz, another surgeon working in Budapest, made modifications and improvements on the original and his instrument of 1920 was still in use through the fifth and sixth decades of this century. The Russians are generally acknowledged as improving these instruments in the 1950s and, with the additional modifications of M. M. Ravitch, their use has spread and they have become widely utilized in the United States.

The stapling procedure, both in closing bowel and in anastomoses, involves placement of double, overlapping rows of B-shaped fine wire staples. The particular shape of the staple insures an adequate blood supply to the bowel edge. The initial acceptance and success of the gastrointestinal anastomosis (GIA) and the thoracicoabdominal 30-mm, 55-mm and 90-mm (TA 30, 55 and 90) instruments in facilitating division, closure and anastomosis of various portions of the gastrointestinal tract were followed by the development of the end-to-end anastomosis (EEA) and intraluminal stapler

(ILS) circular anastomotic instruments and finally the production of all of these in a disposable form. The EEA and ILS instruments, in particular, have been beneficial in that very low colorectal anastomoses can now be done in patients who previously had to have abdominoperineal resections. Additional applications have been found for these circular staplers in upper colon, gastric and esophageal procedures.

Other stapling devices have received somewhat less widespread acceptance, for example, ligating and dividing staplers, fascial staplers and skin staplers.

It has been claimed that stapled anastomoses can be done more rapidly and with less effort on the part of the surgeon than the hand-sewn ones, and thus they are a financial saving because of decreased operating and anesthesia time. Reportedly they lead to better and more rapid healing because of the more adequate blood supply to the edge of the bowel and less trauma from the multiple manipulations of hand sewing. It is also claimed that stapled anastomoses lead to a shorter, less complicated postoperative course from ileus, anastomotic leaks and so forth. Several studies report, however, that operative times and complication rates between the two techniques are not proving to be significantly different. Perhaps these will change as surgeons and surgical teams gain more facility and experience in the use of these instruments.

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Digital Video Subtraction Angiography and Peripheral Vascular Surgical Procedures

PERIPHERAL VASCULAR SURGERY and contrast radiography have shared an important and essential relationship. Whether it be aortic, femoral or carotid arterial occlusion, an endarterectomy or bypass procedure is seldom done without prior angiographic delineation. Despite its widespread usage, arteriography continues to involve a small but potentially serious incidence of adverse complications through embolism or thrombosis, which can lead to limb loss or stroke. For this reason, the diagnostic study of arterial diseases has been supplemented by a vast and rapidly growing noninvasive vascular diagnosis industry. As yet, noninvasive techniques lack precise definition and have not replaced angiography.

Recent developments in computerized digital video subtraction angiography have virtually eliminated the more serious risks of arteriography by avoiding intraarterial catheterization. The method originally described by Robb and Steinberg in 1939 has been supplanted by more recent advancements in computer technology. This new technique essentially separates and amplifies the signal from iodine contrast medium injection to the artery, resulting in improvement of image resolution and obviating the need for intraarterial catheterization. The basic process involves storage of the image of the arterial field in digital memory before injection of the contrast medium. Subsequent images following iodine dye injection are sequentially subtracted by computerized digital video image processing. The subtracted images of the arteries thus obtained are enhanced by the contrast medium and the final displayed image is available on video tape or on a standard photograph. The radiation exposure is comparable to standard angiography. Although relatively minor defects such as patient motion, dye extravasation or inadequate venous access may require refinement, this technique, by providing precise arterial definition, is now practical, acceptable clinically and shows promise in areas of vascular diagnosis currently primarily screened by noninvasive studies.

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Home Parenteral Nutrition

HOME PARENTERAL NUTRITION has become a readily available and effective therapy for a select group of patients who might otherwise die or be disabled for lack of a functional small intestine. Originally introduced by Scribner and Cole in 1970 as an "artificial gut," the technique has since been reported in more than 500 patients—neonatal through geriatric—and is no longer considered experimental.

Candidates for home parenteral nutrition include well-motivated patients who have massive small bowel resection, radiation enteritis, intractable small bowel fistulas, severe small bowel mucosal disease, pseudoobstruction and some adults and many children with intractable Crohn's disease. Before home parenteral nutrition is begun, patients should be evaluated for surgically correctable disease and considered for home enteral nutrition.

The standard treatment has three stages. First, total parenteral nutrition is initiated in hospital until metabolic parameters are stable. Second, thorough instruction is given to the patient or parents in aseptic technique, details of the infusion and potential complications. The third phase is outpatient management. Though initial stabilization and teaching are still probably best done at a medical center with a multispecialty team committed to maintaining a home parenteral nutrition program, patients usually return home for long-term management.

Though catheter-related sepsis remains a problem, advances in vascular access techniques and solution

preparation have decreased risks. The best results have been reported using central venous placement of a silastic catheter (Hickman or Broviac) with a subcutaneous tunnel and a Dacron cuff to prevent ascending infection. The catheter may be placed using local anesthesia via cutdown or simply percutaneous subclavian placement through a breakaway introducer. Preformulated home total parenteral nutrition solutions are available, though many long-term patients may be taught to safely prepare solutions at home with a greatly decreased cost and a heightened feeling of independence.

Benefits are significant. In adults normal body composition and weight develop and in children with Crohn's disease and in neonates, normal growth patterns develop. Most patients are able to obtain adequate nutrition by continuous infusion while sleeping and may resume normal activities during the day; in one report, 70 percent of patients returned to usual employment. Costs of approximately $20,000 a year are significantly less than in-hospital therapy and complications have been much less frequent than that generally reported for in-hospital parenteral nutrition.

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Carotid Endarterectomy

ENDARTERECTOMY of the common carotid bifurcation has become established as a popular operation, with 40,000 done annually. It has a low risk, averaging 2 percent to 3 percent combined morbidity and mortality in most experienced centers.

Its role in the treatment of transient ischemic attacks is well accepted. The role in the treatment of asymptomatic lesions is less clear. Tight stenoses, bilateral stenoses and large or compound ulcers (which are better described as compound deformities rather than ulcers) are being accepted as anatomic indications for operation. The large compound ulcer is associated with a stroke rate of 7½ percent per year; even intermediate (type B) ulcers have a rate of 4½ percent per year. Combined, their average is that of the risk rate of stroke in the presence of transient ischemic attacks, though the risk of an ulcerative lesion increases with time instead of being maximal in early follow-up years.

Noninvasive evaluation of the carotid artery has become increasingly sophisticated and shows promise of increasing accuracy in identifying ulcerated, nonstenotic lesions. The usefulness of noninvasive evaluation of a symptomatic carotid lesion is limited, however, and negative findings from noninvasive studies should never preclude arteriography in a symptomatic patient. The real clinical role lies in the evaluation of asymptomatic lesions and in following patients after operation.

Digitalized subtraction angiography has not yet fully supplanted noninvasive or physiologic studies or classical arteriography.

In the conduct of the operation itself, the use of the shunt remains debatable. Its use is generally accepted in the presence of stump pressures below 25 torr, when serious stenosis exists contralaterally, and in poststroke patients. Some surgeons, however, never use the shunt. Few surgeons use patches except in very small arteries and, as a rule, use only autologous tissue.

Open operative dilatation of difficult-to-reach fibromuscular lesions is now standard, but percutaneous transluminal angiography is not acceptable because of its inherent risk of distal embolic formation.

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Vascular Access for Treatment of Acute Renal Failure

ALTHOUGH THE Quinton-Scribner arteriovenous shunt remains the most widely used form of vascular access for acute hemodialysis, there exists a significant number of patients for whom this procedure is not well suited. This group is often better served by some form of venovenous access. Such access usually requires placing two catheters into the iliofemoral venous system using the Seldinger technique. It is even possible to use single-needle dialysis equipment that alternately removes and returns blood through one cannula.

The venovenous method has become the preferred method when there are contraindications to the use of an arteriovenous shunt. Hemodynamically unstable patients present several problems. Hemodialysis tends to cause episodes of hypotension with poor blood flow from the arterial cannula. Also in such patients thrombosis frequently develops in their arteriovenous shunts between dialyses. With venovenous access flow can be maintained during hypotensive periods and catheters are usually removed between treatments. Patients in whom renal recovery is unlikely to occur should have venovenous access, because the use of an external arteriovenous shunt limits the sites available for the more durable subcutaneous access necessary for ongoing hemodialyis. Some patients lack the vasculature necessary for Quinton-Scribner shunts because of arteriosclerosis, drug abuse, major burns or use for intravenous or intraarterial cannulas. Finally, because of the simplicity and greater ease of placement in the setting of an intensive care unit, patients who are likely to require only one or two dialysis treatments (for example, drug overdose patients) are best served by venovenous dialysis.

There has been some concern regarding thromboembolic complications with repeated femoral vein catheterization, particularly when catheters are left in place.

Additional utility was introduced by Flynn and McGowan when the single-needle technique was applied to the subclavian vein approach, allowing the cannula to be left in place for several weeks. Yet there has been concern with the tendency for single-needle dialysis to recirculate the same blood and such equipment is not always available or functional. These limitations have led to the development of a double-lumen coaxial catheter suitable for subclavian cannulation, allowing hemodialysis through a single #8 French catheter (Vas-Cath, Shiley). This steadily increasing variety of vascular access for patients requiring exigent dialytic therapy provides valuable flexibility.

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Gastric Mucosal Erosion

GASTRIC MUCOSAL EROSION in seriously ill patients is defined as multiple, superficial mucosal defects that occur with serious illness from sepsis, trauma, respiratory failure, uremia or shock. The underlying pathophysiology is obscure and varied and includes such different entities as Curling's ulcer in burn patients, Cushing's ulcers, ulcer occurring from administration of various drugs such as aspirin and alcohol, reflux of bile and the "ICU syndrome" or that which occurs in seriously ill patients in surgical intensive care units. The incidence of ulceration or bleeding from such ulcers (or both) is variable and has been estimated to occur in anywhere from 3 percent to 6 percent of patients who are seriously ill to upwards of 54 percent of patients with intracranial disease, the diagnosis being made by endoscopy.

Over the years the incidence of upper gastrointestinal bleeding from acute gastritis and acute stress ulceration appears to be decreasing. Many of the factors attributed to this decreased incidence are greater attention to appropriate nasogastric drainage, intensive replacement of fluids in burn trauma and seriously ill patients and improved respiratory management. Particularly important has been the attention to better nutritional support, the advent of intravenous administration of hyperalimentation and the widespread occurrence of routine intragastric alkalinization. Despite the presence of gastritis in acute mucosal lesions, few of these patients (less than 20 percent) ever bleed to the point where they require operative intervention.

Maintaining the gastric luminal pH at 7.0 with antacids has resulted in a decreased incidence of ulceration in seriously ill patients. In a prospective study by Priebe and Skillman in 1980, findings in a group of patients treated with antacids were compared with those in a group treated with cimetidine. In 37 patients receiving antacids, no bleeding was noted as opposed to an 8 percent bleeding rate in those given cimetidine. Other studies have indicated no differences in prophylaxis between cimetidine and antacids and that using one or the other was significantly better than no treatment. Zinner and associates noted that the benefit of antacids over cimetidine was greatest among those patients with the greatest number of risk factors. It was apparent that antacids more satisfactorily achieved adequate pH control ($pH > 3.5$).

Once bleeding occurs, a wide range of nonoperative approaches has been used, such as continued antacid installation and administration of cimetidine, along with iced gastric lavage and localized gastric cooling. Others have advocated the use of endoscopic electrocoagulation or endoscopic coagulation with a laser or both. Prostaglandin has been shown in studies using animals to have some promising usefulness but is not yet available for human use. Evidence exists that vasopressin given intravenously has a similar effect to intraarterially administered vasopressin. The effectiveness of vasopressin on the rate of bleeding from acute gastritis is variable. Recurrent bleeding is the rule and using vasopressin rarely alters the decision to operate.

When surgical intervention becomes necessary, a variety of procedures have been advocated, with a more extensive operation such as gastric resection or total gastrectomy having the greatest mortality and morbidity. Vagotomy and pyloroplasty with suture ligation of the bleeding site has the best overall clinical effect with the lowest mortality. Satisfactory cessation of bleeding, however, is usually achieved only when actual suture of a bleeding site is possible. Recurrent bleeding is generally best managed by a total or near-total gastrectomy. The percentage of patients requiring operation has continued to drop as advances are made in adequate prophylaxis.

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Infection in Burn Patients

BARRIERS AGAINST INFECTION of a burn wound include asepsis, antisepsis, prompt burn excision and wound closure, effective nutrition, either prophylactic or therapeutic (or both) use of systemic antimicrobial agents and immune factors.

Whereas sterile laminar airflow plus barrier isolation has been reported in one or two centers to prevent cross-infection, no definitively controlled study has yet confirmed this or shown the cost-effectiveness of this aseptic technique. In experimental studies using animals, *Aloe vera* applied topically appears promising for its antimicrobial properties and in preventing progressive burn ischemia, but it remains inadequately

tested for use in humans. Silver sulfadiazine cream remains the most popular topical agent in use, 0.5 percent silver nitrate solution and mafenide acetate cream being appropriate in special circumstances. Prompt excision and autografting of third-degree burns has been associated with reduction in hospital stay and mortality in several categories of patients, but requires considerable experience to be consistently safe and effective in very large burns. Fresh split-thickness allograft skin remains the best tested autograft substitute, but several artificial skin substitutes have proved useful in special circumstances, and some may prove to have advantages (like the absence of immunologic rejection in scar formation) not present in allograft skin.

Maintenance of body weight and nitrogen balance using enteral nutrition with an unusually high kcal-to-gram nitrogen ratio (about 100:1) is associated with improved survival, at least in children and probably also in adults. Prophylactic intraoperative administration of antibiotics is standard therapy during excision of large burns. Routine use of prophylactic antistreptococcal antibiotics on admission has been questioned, however, though no harm or development of antibiotic-resistant bacteria has been noted.

Finally, while a very promising area of sustained and intensive research, mortality and morbidity due to monocyte, lymphocyte, polymorphonuclear leukocyte or humeral immune abnormalities (or all of these) remain unaltered in large human burns except for nonspecific and indirect measures such as those noted above.

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Ascites and the Peritoneovenous Shunt

ASCITES is an often difficult-to-manage, potentially lethal complication of advanced liver disease. Its precise pathophysiology remains undefined. Increased portal pressure and decreased oncotic pressure allow transudation of lymphatic fluid into the peritoneal cavity, causing ascites. This fluid shift reduces effective plasma volume, which then stimulates the renal renin-angiotensin-aldosterone mechanism to preserve sodium and water. Strict sodium and water restriction, judicious use of loop diuretics and giving aldosterone inhibitors will control ascites in most patients. However, some become totally refractory to such therapy or oliguria, azotemia, encephalopathy or hepatorenal syndrome develops. Previously, treatment of such refractory ascites by paracentesis and ascitic fluid infusion or the use of Holter-type peritoneoatrial shunts resulted in temporary improvement only. Portacaval shunt remained the only effective surgical treatment, presumably acting by reducing portal pressure.

In 1972 LeVeen introduced a one-way, pressure-activated valve or peritoneovenous shunt, which permits continuous infusion of ascitic fluid into the superior vena cava. This valve opens with a pressure gradient of 2 to 4 cm of water. The apparatus can be inserted under local anesthesia. The collection tubing is placed in the peritoneal cavity; the valve is seated under the abdominal wall muscles, and the venous outflow tubing is led subcutaneously and passed through the internal jugular vein into the superior vena cava. Respiration activates the valve. Diaphragmatic descent during inspiration causes a rise in intraperitoneal pressure and a reduction in intrathoracic pressure, resulting in a greater than 4 cm gradient across the valve. The valve then opens, fluid passes from the abdomen to the superior vena cava, blood volume increases and diuresis occurs. If blood volume increase exceeds diuresis, the central venous pressure rises, the gradient drops and flow ceases.

Rapid diuresis with increase in renal blood flow, glomerular filtration and sodium excretion follow successful peritoneovenous shunt insertion. However, complications may occur. Meticulous surgical technique is necessary to avoid ascitic fluid leak, sepsis or immediate mechanical shunt failure. Progressive fibrin deposition may cause delayed shunt failure. About a third of peritoneovenous shunts require revision. Complications from this shunt include pulmonary edema, diffuse intravascular coagulation, superior vena cava thrombosis and bacterial peritonitis. Such complications may require shunt ligation or removal.

Despite these problems, continued experience with this shunt has confirmed its efficacy in selected patients who have cirrhotic ascites, endophlebitis hepatica obliterans (Budd-Chiari syndrome), chylous ascites, pancreatic ascites and malignant, cardiogenic and nutritional ascites. It may be of benefit in some patients with hepatorenal syndrome. Relative contraindications to a peritoneovenous shunt include patients with severe alcoholic hepatitis and jaundice, severe encephalopathy, variceal hemorrhage, acute tubular necrosis, peritoneal sepsis, coagulation disorders and heart failure. Recent technical innovations include the Denver peritoneovenous shunt, which permits various flow rates, and the temporary external Silberman shunt, used in patients with acute ascites.

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Preoperative Nutrition Therapy

MANY OBSERVATIONS support the concept that poor nutrition has an adverse effect on the postoperative course of surgical patients. In 1936 Studley reported a tenfold increase in postoperative mortality among patients treated for intractable peptic ulcer disease who

had sustained a preoperative weight loss of 20 percent or more.

More recently other parameters that are influenced by nutritional status also have been correlated with postoperative morbidity and mortality. Thus, serum albumin levels less than 3 grams per dl and transferrin levels less than 220 mg per dl are associated with a significant increase in the incidence of postoperative complications, and similar adverse effects are observed when patients exhibit impaired reactivity to a panel of standard skin test antigens such as purified-protein derivative (PPD), mumps, streptokinase-streptodornase, *Candida* and *Trichophyton*. A nearly eightfold increase in postoperative mortality and a fourfold increase in postoperative sepsis were reported by Pietsch and associates among surgical patients who failed to react to any of these five antigens before undergoing operation. Furthermore, when sequential skin testing indicates an improvement in immune reactivity, a reduced incidence of complications is observed.

These putative nutritional measurements are relatively insensitive indicators, however, and are subject to a variety of nonnutritional influences that may confound interpretation. In addition, prolonged starvation is not a prerequisite for the development of adverse clinical consequences; significant functional abnormalities have been observed after only ten days of nutritional deprivation.

Available data lead logically to the hypothesis that improving the nutritional state before a surgical procedure should have a salutary effect on the postoperative course. Only recently, however, has the effect of preoperative nutritional therapy been subjected to careful investigation. Many studies indicate that nutritional indices can be maintained or improved by intensive nutrition therapy, but the effect on postoperative morbidity and mortality has been variable. Total parenteral nutrition given for less than five days preoperatively is of little benefit. However, malnourished patients with inflammatory bowel disease who receive at least five days of total parenteral nutrition are found to have significantly fewer postoperative complications than those patients who do not receive this treatment.

Mullen and co-workers evaluated the effect of at least seven days of preoperative administration of total parenteral nutrition on the postoperative course of a group of patients deemed to be at high risk for the development of complications because of malnutrition. This high-risk group was identified by calculating the patients' prognostic nutritional index, a computer-generated regression equation taking into account serum albumin and transferrin concentrations, triceps skinfold thickness and delayed-hypersensitivity skin test reactivity. Preoperative administration of total parenteral nutrition was associated with a 2.4-fold reduction in all complications, a nearly sevenfold reduction in the incidence of major sepsis and a fivefold reduction in mortality. No benefit was observed, however, in the less severely malnourished patients.

In a recent randomized trial, Muller and colleagues observed a significant reduction in the rate of postoperative mortality and major complications (defined as intraabdominal abscess, peritonitis, anastomotic leakage and ileus) among patients with carcinoma of the esophagus, stomach, colon, rectum or pancreas who received total parenteral nutrition providing 37 kcal per kg of body weight a day for ten days before operation. The control group was offered a regular 2,400-kcal hospital diet. The investigators attributed the salutary clinical results to the improvement in humoral and cellular immunocompetence and protein status that was observed in the total parenteral nutrition-treated group. It is important to note that a deterioration in these nutritional indices occurred in patients in the control group, evidently due to medical conditions or diagnostic procedures that precluded consumption of the oral diet offered.

Thus, current information suggests the value of administering total parenteral nutrition for at least five to ten days before an elective operation for patients who are malnourished or for normally nourished patients in whom a lengthy preoperative evaluation may interfere with adequate oral intake.

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Carcinoma of the Pancreas

CARCINOMA OF THE PANCREAS is the eighth most frequently occurring cancer and the fifth most common cause of death from cancer in the United States. Since 1937 the incidence of the disease has increased in the United States and Europe. Tobacco, diabetes and diet have been incriminated as factors associated with increased risk of pancreatic carcinoma. While coffee was incriminated as a factor in one report, its causal role in the development of pancreatic cancer has been vigorously challenged from other sources. That coffee has any role in the development of pancreatic cancer remains an unproved assertion at this time.

There is still no feasible screening test for cancer of the pancreas which would permit early detection of this highly aggressive tumor that has a median survival of 3.3 months after histologic confirmation and a one-year survival of 11.9 percent. However, once carcinoma of the pancreas is suspected on the basis of clinical findings, powerful diagnostic tools are now available to confirm its presence. These are transhepatic cholangiography, endoscopic retrograde cholangiopancreatography and, to a lesser extent, ultrasonography, angiography and computerized tomographic scan. A preoperative histologic diagnosis can be established by

thin-needle biopsy, but in smaller lesions that have the best opportunity for resection the tumor may be missed. Therefore a percutaneous needle biopsy of the pancreas in which the findings are negative for tumor does not rule out carcinoma of the pancreas.

Five-year cures of pancreatic carcinoma are still rare and are usually associated with lesions in the head of the pancreas where common bile duct obstruction occurs early. Lesions of the body and tail seldom come to attention until they have spread beyond the confines of the pancreas. Pancreatoduodenectomy remains the best palliation for the 15 percent to 20 percent of patients found to have resectable lesions in the absence of metastases. The hope that more extensive resections such as total pancreatectomy would provide improved cure rates has proved to be unfounded. The addition of vagotomy at the time of pancreatoduodenectomy does not seem to reduce the incidence of peptic ulceration and gastrointestinal hemorrhage in patients undergoing pancreatoduodenectomy for cancer.

The 40 percent to 50 percent of patients with metastasis or locally unresectable cancer of the pancreas, most of whom are jaundiced but well enough to undergo celiotomy, are best managed by the simplest biliary bypass possible, that is, cholecystojejunostomy and chemical splanchnicectomy with administration of a solution of 15 ml of 6 percent phenol or 100 percent alcohol to provide pain relief. There is no evidence that the incidence of cholangitis is less with either Roux-en-Y cholecystojejunostomy or choledochojejunostomy. Most authors advocate gastrojejunostomy at the time of biliary bypass, otherwise 20 percent of patients will require a second operation for gastric outlet obstruction. There is a high incidence, about 20 percent, of gastrointestinal bleeding after biliary bypass in patients with pancreatic cancer. In many of these patients, the gastrointestinal bleeding is a major contributor to the death of the patient. The cause of peptic ulceration and bleeding in these patients is believed to result from the diversion of bile from the duodenum in patients whose gastrointestinal tract has already been deprived of pancreatic secretion as a result of tumor obstructing the proximal pancreatic duct.

The use of percutaneous transhepatic tube decompression of the obstructed common duct can be helpful in improving liver function in patients being prepared for resection who have been jaundiced for more than a month.

Percutaneous transhepatic decompression is not a substitute for operative biliary and gastric bypass and chemical splanchnicectomy except in a patient too ill to undergo celiotomy. A further disadvantage of percutaneous transhepatic decompression is that some patients with curable ampullary or distal common bile duct lesions who have a much more favorable prognosis than patients with pancreatic cancer may not be identified and resected. An additional disadvantage of percutaneous transhepatic decompression in patients with carcinoma of the pancreas is that the incidence of cholangitis is higher than after operative cholecystojejunostomy.

Chemotherapy with present regimens has not provided appreciable prolongation of life in patients with pancreatic cancer, though with some of the more recent combination chemotherapy the incidence of response has reached the 40 percent level.

Irradiation with heavy ions that can be better focused and have greater penetration has shown some promise with or without adjunctive chemotherapy in patients with locally unresectable lesions. However, the number of patients treated with these modalities has been small and a somewhat selected group. Radiation therapy with interstitial implants into the primary tumor is also being used but is a very cumbersome and logistically difficult technique to carry out in the operating room. The combination of irradiation and chemotherapy seems to have shown the greatest number of patients surviving as long as 40 months.

Local heating of tumors by ultrasonic or diathermic means has not yet proved applicable to the pancreas.

In summary, there is a need for a tumor marker to assist in screening the at-risk population. All attempts at cure of pancreatic cancer to date have to be considered, at best, palliative measures. Pancreatoduodenectomy offers the best palliation in patients who have small localized lesions without metastases. The procedure can only be justified if the mortality is low and should therefore not be done by an occasional operator.

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Trauma Care—Recent Advances

TRAUMA, defined as accidental or intentional injury, is the most common cause of death in persons aged 1 to 38 years. The death rate for trauma in the age group 15 to 24 has risen from 106 per 1,000 in 1968 to 120 per 1,000 in 1978. During that same period, the overall mortality for persons aged 25 to 64 declined 16 percent. Trauma mortality in the United States is 50 percent higher among American teenagers than for teenagers in Sweden, England and Japan combined. The estimated cost of death and disability due to trauma is in excess of $228 million annually. Only recently has information become available that allows rational evaluation of the potential efficacy of different aspects of the emergency health care system.

Concerning prehospital care, improvement in transportation and training of ambulance personnel has resulted in identifiable benefits in some areas of emergency

illness, particularly cardiac arrest from coronary artery disease. Of the 650,000 people who die of arteriosclerotic heart disease annually (primarily from coronaries), upgrading the training of ambulance personnel from emergency medical technician to paramedic service has resulted in a 10 percent increase in survival (that is, of 100 cardiac arrests, an additional 10 lives have been saved, an improvement from 7 percent to 17 percent). In cardiac arrest from coronary artery disease, an ambulance response time of less than two minutes will allow 55 percent of patients to be admitted to hospital, whereas if the response time is eight minutes, only 19 percent will survive long enough to be admitted to hospital. The comparable discharge survival data are 33 percent and 12 percent, respectively. The improvement in survival of a cardiac arrest victim from coronary artery disease has been in the range of 10 percent. Because about 25 percent of these patients sustain cardiac arrest acutely, the net potential benefit of prehospital care is an improvement in survival of 2.5 percent (25×10) of all cardiac arrest victims.

Extrapolation of data on cases of cardiac arrest from coronary artery disease to trauma cases is inappropriate. Although it is attractive to assume that more training and utilization of on-site equipment such as pneumatic antishock garments (military antishock trouser, or MAST suits) should produce improvement in the care of patients with severe injury, no data exist to prove this thesis. Information is beginning to emerge that establishes that transport delays for purposes of on-site resuscitation are associated with excessive mortality if the injury is life threatening. For example, in one study evaluating traumatic injury to the heart, there were no survivors among patients in whom field resuscitation with concomitant prolonged prehospital delay occurred. If prompt transport of victims with heart wounds occurs, a 20 percent to 30 percent survival is possible. Similar findings for other types of severe injuries associated with hemorrhagic shock are applicable when the availability of prompt and appropriate care is within a 15- to 20-minute transport time. In patients with less acute but equally life-threatening injuries, a "golden interval"—usually less than an hour—is best spent in transportation to a trauma center after stabilization of fractures and initiation of intravenously given fluid therapy.

Maximal use of the first hour after injury depends on geographic considerations. In areas of dense population with short distances to a trauma care center, such as in San Francisco, ground transportation is the optimal transport means. In rural areas, such as the Imperial Valley (south central California), rotary or fixed-wing transport to a trauma care center has resulted in a substantial improvement in mortality for injuries of comparable magnitude, when victims are rapidly moved to definitive care, rather than receiving initial extensive prehospital and "nearest hospital" care.

Studies done in California and elsewhere speak to the need for continued definition of a regional system of trauma care, as defined by the report "Categorization of Emergency Facilities and Trauma Centers" by the Committee on Trauma of the American College of Surgeons. Several studies have shown that 30 percent to 35 percent of trauma deaths are potentially salvageable, if treated in a trauma center. The absence of a system for transportation and care of trauma victims and the persistence of the "nearest hospital" concept continue to result in unnecessary death after injury. The increasing tendency for transport delay for purposes of extensive field resuscitation is contributing to this problem.

Because about 5 percent of motor vehicle injuries are critical, a system to minimize the death rate from such injuries is necessary. Because as high as 50 percent of deaths from injury occur *after* the patients reach the hospital, continual evolution of trauma care centers, appropriate prehospital care, proper transportation systems and development of new trauma care centers are mandatory.

It is now apparent that trauma care centers can improve mortality from injury. Because transportation systems are available to bring patients to a trauma care center, emphasis should be placed on rapid transport and not on field resuscitation.

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Parathyroid Autotransplantation

THE SUCCESS AND SIMPLICITY of parathyroid autotransplantation favors the use of this technique in standard surgical practice for those patients who stand to lose all parathyroid function as a consequence of a neck exploration or in whom residual or in situ parathyroid tissue has a good likelihood of becoming hyperactive. The principles of parathyroid transfer are the same as those for other grafts without a vascular pedicle such as a split-thickness skin graft in that the graft will be profoundly ischemic until capillary perfusion begins in three to five days. During this time the tissue is nourished by diffusion only. The graft will succumb to ischemia if vascular ingrowth is delayed by such factors as low perfusion pressure, regional scar, hematoma or infection. However, a split-thickness skin graft is prepared to function as an epithelium within 10 to 14 days of grafting while the endocrine epithelium of parathyroid tissue temporarily loses function during the three to five days when only diffusion is providing metabolic exchange. This diffusion support is only adequate for subsequent survival if the parathyroid graft is reduced to fragments no larger than 1 to 2 mm in diameter. The subsequent function of the graft will not be evident

until the endocrine epithelium has been regenerated on the interstitial matrix. This may take as long as three months. If the patient is dependent on the graft, calcium and vitamin D supplementation are required during the accommodation phase of engrafting.

Dr Sam Wells of Washington University (St Louis) has accumulated the largest number of cases of parathyroid grafting and a review of his series clarifies the indications for the procedure. Patients who have multiple endocrine adenopathy or secondary hyperparathyroidism have a high rate of recurrence and therefore reexploration procedures of the neck. The hazards of repeat neck operations are well recognized and can be avoided by removing all parathyroid tissue from the neck at the time of the first exploration. Patients who must have a repeat neck exploration can present even greater difficulty in identifying normal parathyroid tissue than in locating the abnormal tissue causing the recurrent or persistent disease. The risk of permanent hypoparathyroidism is best managed by transplanting 30 mg of parathyroid tissue to a site more accessible than the paratracheal region. Patients who require a total thyroidectomy for carcinoma have always been at risk for hypoparathyroidism because the blood supply to the thyroid gland is shared by the parathyroids and wide excision for thyroid carcinoma can destroy the parathyroids by infarction. This potential parathyroid loss is well managed by autotransplantation. The following are clear indications for parathyroid autotransplantation: (1) multiple endocrine adenopathy and (2) secondary hyperparathyroidism because of high likelihood of recurrence; (3) reexploration of the neck, and (4) total thyroidectomy because of the risk of hypoparathyroidism.

The grafting technique is not difficult. The parathyroid tissue is finely minced to 1-mm fragments for grafting. About 30 of these fragments are transferred to the brachioradialis muscle. Pockets are created among the muscle fascicles and after careful hemostasis four to five tissue fragments are placed in each. The muscle is closed, with each site marked with a nonabsorbable suture. An interesting feature is that the transplanted tissue need not be *normal* parathyroid. Hyperplastic tissue has shown little tendency to excessive function if no more than 30 mg is transplanted. The function of the graft is monitored by comparing the parathormone levels in the antecubital vein of the grafted and the ungrafted arms. After two months the parathormone level usually suggests function and the vitamin D and calcium support can be sequentially withdrawn. Autotransplantation was successful in 92 percent of the patients of Wells and colleagues who had primary hyperparathyroidism and in all patients managed for total thyroidectomy. Cryopreservation of parathyroid tissue has been extremely useful, such that an inadequate graft can be supplemented with preserved autologous tissue. Rarely, the graft will release excessive parathormone and this can be corrected by removing two to three of the pockets of transplanted tissue. The excision can be conducted under local anesthesia in an outpatient setting.

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Adrenalectomy for Metastatic Breast Cancer: Surgical Versus Medical Treatment

ONE OF THE MOST IMPORTANT FACTORS associated with an improved prognosis in metastatic breast cancer is the presence of estrogen-receptor protein in the tumor cell cytoplasm. Some 50 percent to 60 percent of patients with estrogen-receptor-positive tumors respond to oophorectomy or to antiestrogen therapy such as the administration of tamoxifen citrate. In addition to the presence of estrogen receptors, additional factors that affect a favorable prognosis include a long disease-free interval, a good response to previous endocrine therapy and metastatic tumor involvement limited to soft tissue and bone. Of women who have responded to oophorectomy or antiestrogen treatment, 30 percent to 40 percent will respond to a subsequent surgical adrenalectomy.

Aminoglutethimide is a compound that was initially developed as as anticonvulsant and later found to be an inhibitor of adrenal steroid production. Aminoglutethimide blocks the conversion of cholesterol to Δ^5-pregnenolone at the beginning of the biosynthetic pathway, blocking the production of cortisol, androgens, estrogens and aldosterone. There is an additional blocking of estrogen in the peripheral tissues by the inhibition of androstenedione conversion to estrone and estradiol. With suppression of the adrenal gland, there is a fall in cortisol levels and a rise in adrenocorticotropic hormone level that can overcome the aminoglutethimide blockade unless a glucocorticoid is also given. Most patients will have maximal estrogen suppression with administration of aminoglutethimide, 250 mg given by mouth four times a day, together with 40 mg of hydrocortisone in divided doses (10 mg in the morning, 10 mg in the afternoon and 20 mg at bedtime). Due to occasional salt-loss problems, supplementation with a mineralocorticoid (fludrocortisone acetate, 0.1 mg given twice weekly) may be required, particularly during hot weather. Early side effects with the drug are common but usually subside in two to three weeks. The side effects are ataxia, lethargy, dizziness, visual blurring and a pruritic maculopapular rash. These side effects usually do not warrant an alteration in medication because they tend to be self-limited. Occasional cases of hypothyroidism have been described, as have rare blood dyscrasias.

The medical adrenalectomy regimen of aminoglutethimide plus glucocorticoids in a study of 50 postmenopausal patients with metastatic breast cancer showed a

38 percent complete or partial remission and stabilization of disease in 20 percent, with 12 percent of the latter group having symptomatic relief of bone pain. This group compared favorably with historical controls treated by adrenalectomy. A randomized prospective trial comparing surgical adrenalectomy with aminoglutethimide and hydrocortisone therapy also revealed medical adrenalectomy to be as effective as surgical adrenalectomy. In this group, 53 percent of 40 women treated with medical adrenalectomy had objective responses compared with 45 percent of 29 women undergoing surgical adrenalectomy (no significant difference). Treatment response was 17.2 months in the medically treated group and 17.1 months in the surgical group.

Medical adrenalectomy appears equal to surgical adrenalectomy in terms of response rate and duration of response. A major advantage of medical adrenalectomy is its reversibility and a lack of major side effects. Surgical adrenalectomy is not reversible and has a significant morbidity and mortality. Surgical adrenalectomy in patients with metastatic breast cancer should be reserved for those who are unable to take aminoglutethimide and hydrocortisone because of untoward side effects or drug reaction.

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Editorials

Of Dictators and Czars in Health Care and Elsewhere

In June of 1982 the California legislature acted essentially without any public discussion or review to give one person unprecedented authority to negotiate and award contracts to hospitals and other organizations to provide health care for Medi-Cal patients. Medi-Cal is California's name for its Title XIX or Medicaid program. The authority to make contracts appears to be absolute and the negotiations for them have been conducted in secrecy. Things have moved rapidly and many contracts were to become operative on January first.

The scenario that must have occurred seems to have been somewhat as follows: For many reasons, not the least of which has been additional entitlements to Medi-Cal benefits authorized by the legislature over the years, the cost of the program has been rising while the revenues to the state did not keep pace with these and other legislatively mandated expenditures. A crisis occurred when the legislators recognized that the Medi-Cal expenditures had gotten so out of hand that they were seemingly beyond control at a time when the legislature was faced with a constitutional requirement to balance the state budget. In what must have been an atmosphere of legislative desperation, Mr William Guy, a person of reputed knowledge and experience in the financing of health care services, evidently persuaded or was persuaded by the governor and the legislature that if he were given the absolute authority he could solve their problems—that is, reduce the cost of the Medi-Cal program. He was given the authority and is now called the "Medi-Cal czar." How well the problem is solved remains to be seen.

There has long been a school of thought that when in a free society things get so out of hand as to seem unmanageable, a people will eventually become frustrated and frightened enough to turn to and follow someone who is sufficiently self-confident and charismatic to convince them that he has the answers and can solve the problems if they will just give him the authority and let him do it. Dictators have been created by the legislative process before and have ruled nations. Some of us are old enough to remember when such a process took place in Germany, and more of us are old enough to remember its aftermath. Freedom and the democratic process have been surrendered for what was thought to be certainty or order. To see this happening now, and here, even in one program in health care, gives one pause and certainly much food for thought. Is this really the way we ought to go or want to go in health care, or in the nation for that matter?

—MSMW

Consequences of Nuclear Warfare

The fall 1982 issue of *Daedalus,* the journal of the American Academy of Arts and Sciences, concentrates on the subject of "print culture and video culture." In the preface the editor discusses the "information revolution" of the 20th century. He suggests that there is an "obligation to estimate whether today's information revolution is 'the event of our age,' transcending all others, reducing our century's putative major events—including the two world wars, the Russian Revolution, and the rise of Nazism—to local incidents of substantially less cosmic proportions."

That is one point of view; other people might nominate other great phenomena of our time: air travel, space exploration, despoiling our natural resources, prolongation of the average span of human life from about 45 years in 1900 to about 75 years now and the present growth rate of the world's population.

While these together constitute an argument that our century has witnessed the greatest changes in the history of planet Earth, many of us believe them to be trivial when viewed against the present real possibility of a major war fought with nuclear weapons. As described in this issue of the journal, such a conflict could reduce much of the northern hemisphere to rubble, killing a substantial proportion of the population and destroying governments, order, culture—indeed, the whole fabric of society. Furthermore, the effect of such a conflict on Earth's tenuously balanced ecosystem could threaten to end all life on the planet.

We members of the medical profession cannot ignore such a possibility. As ones whose lives and training are devoted to protecting the health of humankind, we have an obligation to inform ourselves about the facts and to be in a position to help others understand the terrible danger represented by the stockpiling of nuclear warheads in the arsenals of the United States and the Soviet Union, soundless and secret-shrouded.

In recent years organizations such as the Union of Concerned Scientists, the Federation of American Scientists and the National Academy of Sciences have released bulletins that indicate steadily increasing alarm about the possibility and consequences of a nuclear holocaust.

I am convinced this danger is clear and present and do not accept the viewpoint that the medical profession can ignore it, taking refuge in such tired excuses as "It's not our problem; it's too political," or "Our leaders must know things we can't know," or "What about the Russians?" or "Better dead than red."

I believe that members of our profession *can* do something to help bring about a change from the collision course we appear to be on right now. Indeed, at least 15 national medical organizations, including the

American College of Physicians, the American Public Health Association and the Institute of Medicine, have already passed resolutions urging the governments of the two superpowers to spare no effort to extricate themselves from the danger of the nuclear arms race.

Following are some pieces of reading in which I have found invaluable instruction about the nuclear predicament:

Only One Earth—The Care and Maintenance of a Small Planet, written by Ward and Dubos,[1] is an unofficial report from a United Nations Conference on the Human Environment. The authors had input from 150 authorities in many parts of the world. Now about ten years old, the book does not deal exclusively with nuclear war; instead it tells about the interdependence of all living things on our planet, sharing products of the sea, the air and the soil.

The Fate of the Earth by Jonathan Schell[2] does focus on nuclear arms and nuclear war. Some reviewers have described Schell's book as one of the critical pieces of world literature and another calls it the most important book published in 1982. Schell tends to make his points by repetitions in different phrasing, but the total effect is overpowering.

A recent issue of *Ambio* (Vol. 11, Nos. 2 and 3, Pergamon Press, 1982), a "journal of human environment," is devoted to predictions of the aftermath of a nuclear war. The journal, sponsored by the Royal Swedish Academy of Sciences, draws expert contributors from many nations on both sides of the Iron Curtain. The predictions they make about both the short-term and the secondary effects of a major nuclear exchange are sobering, to say the least.

I shall close this editorial note with a tribute that Walter Cronkite paid to one of the physicians' groups working to prevent nuclear war:

It is not pleasant to look death in the face. But unless we do, we are doomed. No group is as qualified to present the terrible facts as these physicians who, with admirable courage and tenacity, have taken into their hands the formidable task of educating the public, the governments and their military to the inescapable results of the nuclear arms folly. To ignore their passionate presentation is to turn our backs on the most urgent issue of our time.

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Reassessing Acid-Base Balance in Hypothermia—A Comparative Point of View

HYPOTHERMIA AS AN adjunct to complex surgical procedures has been used with increasing frequency over the past three decades. In the United States each year, over 100,000 patients have a corrective surgical procedure during cardiopulmonary bypass at low body temperature. Advances in the technology of pump oxygenators and materials in conjunction with the high development of demanding surgical skills and patient management have resulted in remarkable achievements and improving mortality figures. Yet, along with the advantages achieved, hypothermia is accompanied by profound alterations in the physiologic and metabolic states and there may be disturbing alterations in cardiac function and acid-base management problems. In this issue, Dr K. C. Wong presents a brief retrospective of hypothermic procedures and an analysis of the physiology and pharmacology of hypothermia in contemporary settings. This subject is of great interest to comparative physiologists who study the manner in which ectothermic (cold-blooded) animals regulate their internal state as they experience in the course of diurnal and seasonal cycles great variations in body temperature. Conversely, clinicians may find that these lower animals provide patterns of regulation that provoke reassessment of commonly held tenets, particularly in the area of acid-base management.

It has become general practice to apply the acid-base standards of normothermia to hypothermic patients. This is achieved by adjusting gas determinations, such that an arterial carbon dioxide partial pressure ($Paco_2$) of around 40 torr and a pH of 7.4 are achieved at all temperatures. These criteria are based on the concern that a high carbon dioxide partial pressure (Pco_2) may be required to assure adequate cerebral blood flow or—*post hoc, ergo propter hoc*—that values of normothermia are appropriate to all thermal conditions. It will be shown below that these criteria result in a state that is quite hypercapnic and acidotic by ectothermic standards. Thus, the comparative findings are in sharp contrast to those typifying a hypothermic patient.

Before discussing ectothermic acid-base patterns and their biochemical consequences, it is useful to examine the behavior of blood in vitro under changing temperature conditions. Rosenthal[1] found that a specimen of blood sealed from the atmosphere will show a change in pH versus temperature ($\Delta pH/°C$) of -0.015. The slope of pH on temperature is remarkably similar to that of the neutral pH of pure water ($\Delta pH/°C = -0.017$). This parallel behavior led Albery and Lloyd[2] to predict that blood has a dominant protein buffer that has a pK of 7 and heat of enthalpy of 7 kcal. In assessing the various amino acids that could account for this remarkable behavior, Reeves[3] found that only one possessed this property. He has cogently argued that the responsible agent is the imidazole moiety of histidine. Not only does it supply the predicted buffer property, it is present in sufficient concentration to account for the observed pH-temperature slope. It needs emphasis that the slope is preserved across a temperature range *only* under conditions of constant carbon dioxide content of the specimen. This condition prevents titration of imidazole by the bicarbonate system. It is also important to note that in such an in vitro system, the Pco_2 of the specimen will vary directly with temperature.

In general practice, a perfusionist attempts to achieve a pH of 7.4 at low temperature. A specimen of cooled arterialized blood is typically analyzed in an electrode

system whose thermostat is set at 37° C. Thus, if the pH of blood at 25° C is 7.4, the determination made at 37° C will yield a value of 7.2. This reading is then corrected along the Rosenthal curve and the value of 7.4 is reported. Alternately, should a value of 7.4 be found in the 37° C electrode system, a corrected value of pH 7.6 would be reported.

Often overlooked is the fact that a human organism is heterothermic to varying degrees. We indulge in natural experiments during which tissue temperatures become quite heterogeneous. Thus, in great hoards we emerge from nocturnal rest to race about our neighborhoods to strengthen our muscles and tone our cardiorespiratory systems. Such rituals may result in muscle temperatures of 41° C, a skin temperature of 30° C and a liver temperature of 37° C. As arterial blood approaches thermal equilibrium in the precapillary circulation, bearing in mind that the blood is at common carbon dioxide content, the pH will behave *as if* it were in vitro. Thus, in the situation described we may appreciate an array of arterial pH values: liver, 7.4; muscle, 7.34; skin, 7.51. More extreme circumstances may be imagined. This consideration should cause us to question the efficacy of applying normothermic quantitative standards to hypothermic tissues.

The in vivo arterial blood of ectothermic vertebrates exhibits a $\Delta pH/°C = -0.015$, and thus resembles the behavior of in vitro blood at constant carbon dioxide content. In fact, it can be shown that the carbon dioxide content of their arterial blood remains constant across a spectrum of temperatures. Yet, these animals are *open* systems subject to the influence of temperature on metabolism, carbon dioxide production and blood gas transport requirements. The carbon dioxide dissociation curve of blood is importantly modified by temperature such that at a common P_{CO_2} the carbon dioxide content at low temperature will exceed that at a high temperature. The *direct* relationship between P_{CO_2} and body temperature required for constancy of the blood carbon dioxide content is achieved by lung-breathing ectotherms through precise regulation of ventilation. The ratio of ventilation volume to unit production or consumption of a gas is expressed by comparative physiologists as an air convection requirement ($L \cdot mmol^{-1}$). An *inverse* relationship between air convection requirement and body temperature, exhibited by lung-breathing ectotherms, is responsible for the *direct* relationship between alveolar and arterial P_{CO_2}, which is required to stabilize carbon dioxide content over a range of temperatures. This pattern of acid-base regulation exhibited by ectotherms results from the interaction between intrinsic blood-buffering properties and precise respiratory regulation of the carbon dioxide content of the blood. The result is constancy of slope between arterial pH and the pH of neutrality of water and thus constancy of hydroxide ion in relation to hydrogen ion.[4] Thus, at all temperatures there is a constant alkalinity relative to the neutral point of water. Interestingly, Peters and Van Slyke[5] in their classical monograph pointed out that an important feature of mammalian acid-base regulation, one that guards the metabolic integrity of tissues, is the maintenance of a constant alkalinity of arterial blood *relative* to the neutral point! Of course, they were speaking in the context of normothermia.

The significance of this widely occurring pattern of acid-base regulation must be sought at the intracellular level. Studies of intracellular pH show that pH_i-temperature slopes are rather similar to that of the blood. Slopes for heart, liver and smooth and skeletal muscle of turtles lie near the curve of neutral pH of water.[6] A number of enzyme systems, especially those suspected of using histidine-binding sites, have been examined in regard to binding constants or optimal activity. Exemplary of such studies is that of Park and Hong[7] on sodium-potassium-adenosine triphosphatase of various species, which shows that optimal activity follows a $\Delta pH/°C$ of -0.017, that for the neutral pH of water. Among other enzymes showing similar relationships or that manifest conservation of the Michaelis binding constants (Km conservation) are lactate dehydrogenase; acetylcoenzyme A carboxylase; fatty acid synthetase; the reduced form of nicotinamide-adenine dinucleotide (NADH)-cytochrome *c* reductase, and succinate-cytochrome *c* reductase. The relationship of temperature and pH to enzyme function has recently been the subject of review.[8]

Studies by Reeves[9] have emphasized that Donnan's ratio of mammalian erythrocytes is stabilized at various temperatures when extracellular pH is varied, as seen in ectotherms. An accompanying effect is the preservation of constant intracellular volume.

The pattern of acid-base regulation of ectotherms may be generally rationalized in terms of preservation of the efficient behavior of numerous enzymes and stabilization of ion distributions across cell membranes and cell volumes.

Few studies have been specifically designed to examine the potential efficacy of using the ectothermic pattern of acid-base regulation during hypothermia. Taken collectively, the extant studies on animals suggest that this strategy may be a fertile area for further investigation.[10] They indicate that the more alkaline range of pH provided by reduced P_{CO_2} is associated with improvement of myocardial mechanical performance, blood flow and lactate metabolism; increased cerebral and renal blood flows; reduced occurrence of fibrillation, and normalization of calcium flux patterns and improvement in contractility of isolated papillary muscle. Additional references may be found in this issue's article by Wong.

A few clinical studies indicate that the model of acid-base regulation provided by ectotherms may be safely used in humans. Prakash and colleagues[11] ventilated infants at their normothermic level while doing corrective cardiovascular operations during induced hypothermia. This resulted in a direct relationship between arterial P_{CO_2} and temperature and an acid-base pattern similar to that of ectotherms. These researchers conclude that this method is safe and that no adverse

neurologic signs occur on follow-up studies. Blayo and co-workers,[12] using P_{CO_2} control during cardiopulmonary bypass to achieve a $\Delta pH/°C$ of -0.015, clearly showed that the base excesses encountered under conventional conditions (P_{CO_2} of 40 torr, pH of 7.4) were eliminated when using the ectothermic model. Noteworthy was the finding that these patients showed no metabolic acidosis during or following the hypothermic procedures. Dr Wong advocates the practice of not correcting blood gases and pH values read at 37° C. Thus, readings of P_{CO_2} of 40 and pH of 7.4 at 37° C should assure that the blood, at any low temperature, will follow $\Delta pH/°C = -0.015$.

Whereas the lessons of comparative physiology provoke a reassessment of acid-base management practices during hypothermia, it is clearly a time for additional experimental studies that are carefully designed to compare these alternate acid-base strategies. We need to know more concerning the patterns of intracellular pH, regional hemodynamics and the metabolic state of the various tissues and organs under "classical" and "ectothermic" conditions of carbon dioxide and pH management. Especially important will be studies of cerebral hemodynamics and metabolism of animals. It is the hope of this comparative physiologist that the rules of similarity deriving from the study of diverse animals will provoke further investigations from which we may better appreciate the influence of these alternate acid-base strategies on patient welfare. While emphasizing rules of similarity among diverse animals, it is only fair to show an interesting difference: hibernating mammals maintain their arterial pH at near normothermic values!

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Case Reports

Long-standing Angioedema With C1 Esterase Inhibitor Deficiency Associated With Occult Lymphoma

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ACQUIRED DEFICIENCY of the C1 esterase inhibitor protein, which produces a clinical picture closely resembling hereditary angioedema, was first described in a patient with lymphoma by Caldwell and co-workers[1] in 1972. A recent review stressed the importance of differentiating the hereditary and acquired forms of C1 esterase inhibitor deficiency in view of the fact that many patients with the acquired type have underlying lymphoproliferative disease. Other causes include a number of diseases with autoimmune features.[2] In one patient acquired C1 esterase inhibitor deficiency was presumably related to an adenocarcinoma of the rectum.[3] We recently observed acquired C1 esterase inhibitor deficiency in a 43-year-old man with a remarkably long history (six years) of recurrent angioedema who was otherwise asymptomatic. Further evaluation led to the discovery of a non-Hodgkin's lymphoma that may have been indolent during the entire period of his illness. His case is noteworthy for the unusually long prodrome of intermittent angioedema before the diagnosis of lymphoma and further underscores the necessity to distinguish the acquired and hereditary conditions so that specific therapy for the underlying cause of the acquired form may be considered.

Report of a Case

A 43-year-old male minister was referred to Stanford University Hospital in November 1979 for recurrent episodes of angioedema. The attacks had begun in 1974 shortly after a cholecystectomy for gallstones. A presumptive diagnosis of hereditary angioedema had been made in November 1978, based on a C1 esterase inhibitor level of <4 mg per dl (normal 8 to 30 mg per dl). He described attacks of nonpitting edema involving one or several extremities, which resolved completely within four days. He consistently noted malaise and arthralgia for several days before each episode. He said there was no relationship of his symptoms to physical trauma or dental procedures, but considered emotional stress to be a definite precipitating factor. Brief trials of indomethacin and diphenhydramine hydrochloride therapy in 1977 had no effect on his symptoms. Beginning in April 1978, an additional prodrome of crampy abdominal pain and diarrhea developed, which usually resolved after the appearance of extremity swelling. He also had frequent attacks of pharyngeal edema, but these did not result in airway obstruction.

During 1978 the episodes had increased in frequency and at the time of his first Stanford visit were occurring every 10 to 14 days. He said he had neither fever nor weight loss but had had night sweats dating back to 1974. For the past two years he had noted the appearance of asymptomatic papular and nodular lesions on his chest, back and thighs. His past medical history was unremarkable with the exception of a cholecystectomy in 1974, a vasectomy in 1973 and a tonsillectomy in 1958. There was no family history of angioedema, lymphoproliferative or autoimmune disease.

On physical examination numerous bulging, flesh-colored lesions 0.5 to 2.5 cm in diameter were scattered over his shoulders, chest and thighs. Bilateral 1 by 2 cm posterior cervical and left supraclavicular nodes were noted without other lymphadenopathy. There was no extremity or pharyngeal edema. The liver and spleen were not enlarged. No abdominal masses were palpable. The physical examination otherwise showed no abnormalities.

Laboratory evaluation included a C1 esterase inhibitor level by radial immunodiffusion of <4 mg per dl (normal 14 to 30, Scripps Immunology Reference Laboratory, La Jolla, Calif.). Serum C4 was undetectable, C3 was 137 mg per dl (normal 90 to 120) and C1q was <4 mg per dl (normal 14 to 20). All of the above assays were done by radial immunodiffusion. The hemoglobin level was 14.6 grams per dl and total leukocyte count was 6,800 per cu mm, with 53 percent granulocytes, 39 percent lymphocytes, 5 percent monocytes and 2 percent eosinophils. The peripheral blood lymphocyte morphology appeared normal. Urine analysis and tests for erythrocyte sedimentation rate, serum electrolytes, blood urea nitrogen, creatinine, serum aspartate aminotransferase (formerly SGOT), lactic dehydrogenase and alkaline phosphatase gave values within normal limits. The fluorescent antinuclear antibody test was weakly positive (1:80) with a diffuse pattern. The latex fixation test was negative. Serum immunoelectrophoresis showed a monoclonal IgM of *k*-light chain

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type. Free *k*-light chains were detected in a concentrated urine specimen by immunoelectrophoresis. The quantitative immunoglobulins showed IgM of 771 mg per dl (normal 60 to 280), IgG of 535 mg per dl (normal 800 to 1,800) and IgA of 42 mg per dl (normal 90 to 450).

A biopsy of the left supraclavicular lymph node was done. The nodal architecture was overrun by a vaguely nodular proliferation of small lymphoid cells. These appeared to represent an admixture of normal-appearing lymphocytes and slightly larger cells with angulated, irregular nuclear membranes. Germinal centerlike structures were also seen. This was considered to represent lymphocytic lymphoma of intermediate differentiation* as recently defined by Mann and associates.[4] The bone marrow biopsy specimen showed several lymphoid nodules, some of which were paratrabecular in location and some of which were large and composed of round lymphocytes. Biopsy specimens from the soft papular skin lesions showed a loss of elastic tissue of the dermis and moderate perivascular lymphohistiocytic infiltrates that were not considered to represent lymphoma.

Liver-spleen scan showed enlargement of both organs without focal defects. Massive para-aortic and iliac adenopathy was seen on lymphangiography.

Because his episodes of angioedema were frequent and disabling, administration of danazol (600 mg a day) was begun in December 1979 and continued to the present. He had no further attacks of abdominal pain or angioedema. The C4 and C$\bar{1}$ esterase inhibitor levels remained extremely depressed at one and three months after the start of treatment. Because of extensive retroperitoneal lymphadenopathy, treatment for his lymphoma was recommended. He declined chemotherapy and chose to participate in a protocol using fractionated low-dose total body irradiation as a single modality. He was treated with 15 rads of total body irradiation twice a week to a total dose of 150 rads. This therapy was well tolerated and for several months serial abdominal x-rays showed significant reduction of the massive pelvic and para-aortic nodes. However, because of increasing lymphadenopathy combination chemotherapy was begun in March 1981.

Comment

Patients with either hereditary or acquired C$\bar{1}$ esterase inhibitor deficiency have recurrent episodes of nonpitting edema involving the extremities, face, airway and gastrointestinal tract. Low serum levels of the C$\bar{1}$ esterase inhibitor and C4 are features of both conditions and thus these tests are of little help in differential diagnosis. Whereas the onset of symptoms in mid to late life favors the acquired condition, in a few patients who have hereditary angioedema symptoms first develop after the fourth decade. The two disorders can be readily distinguished by measurement of the C1q level because in the acquired deficiency the C1q is profoundly depressed, whereas in hereditary angioedema the level is normal or only minimally depressed.[2] The laboratory findings in our patient (decreased C$\bar{1}$ esterase inhibitor, C4, C1q and the presence of monoclonal IgM) resemble those previously reported in patients with acquired C$\bar{1}$ esterase inhibitor deficiency associated with lymphoproliferative disease.[2] His unusually long history of recurrent angioedema, however, was a point that argued against the presence of an underlying malignancy. In the previous reports of acquired C$\bar{1}$ esterase inhibitor deficiency and lymphoma, angioedema developed within months of the diagnosis of lymphoma.[5,6]

Whereas danazol administration is effective prophylaxis for the attacks of hereditary angioedema, other published articles contain little information on its ability to prevent the episodes of angioedema in acquired C$\bar{1}$ inhibitor deficiency due to lymphoma. In one patient who had asymptomatic C$\bar{1}$ esterase inhibitor deficiency and lymphoma, the C$\bar{1}$ inhibitor level rose to normal after 23 days of treatment with full doses of danazol; the C$\bar{1}$, C4 and C2 levels, however, remained low.[7] In the one patient with rectal carcinoma and C$\bar{1}$ esterase inhibitor deficiency, danazol administration led to resolution of angioedema attacks and normalization of the C$\bar{1}$ esterase inhibitor and complement levels.[3] These levels subsequently fell without evidence of tumor recurrence. In our patient the institution of danazol treatment eliminated the attacks of angioedema but had no measurable effect on C$\bar{1}$ esterase inhibitor, C4 or C1q levels. The drug presumably led to increased synthesis of the C$\bar{1}$ esterase inhibitor[8] and the establishment of a state of compensated consumption of the inhibitor protein. In four previously reported cases (including one with lymphoma), treatment of the underlying disease led to resolution of the episodes.[2] In the present case the C$\bar{1}$ esterase inhibitor and C4 levels remained greatly depressed despite a partial clinical response of the lymphoma to radiotherapy; on danazol therapy he remained free of angioedema, however. It will be of interest to follow the effect of combination chemotherapy on the levels of C$\bar{1}$ esterase inhibitor, C4 and circulating paraprotein.

Acquired C$\bar{1}$ esterase inhibitor deficiency may be more common than previously recognized. The differentiation of this disorder from hereditary angioedema is important for diagnosis, prognosis, therapy and genetic counseling. The lack of a family history does not necessarily indicate the acquired form since in one series of patients who had hereditary angioedema a fourth were unaware of a family association.[9] In most of these cases, studies of asymptomatic first-degree relatives showed the hereditary nature of the defect. Acquired C$\bar{1}$ esterase inhibitor deficiency should be an early consideration in the evaluation of hereditary angioedema-like syndrome with a negative family history. In this setting, noninvasive screening for illnesses known to be associated with acquired C$\bar{1}$ esterase inhibitor deficiency and measurement of the C1q level are indicated. A normal C1q level would point to hereditary angioedema, and subsequent measurement of the C$\bar{1}$ esterase inhibitor level in first-degree relatives would confirm this diagnosis in most instances. Signifi-

*Lymph node material was reviewed by Dr Ronald Dorfman.

cant depression of the C1q level should prompt further evaluation for lymphoma and other conditions associated with the acquired inhibitor deficiency.

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Fulminant Neonatal Hepatic Necrosis Associated With Echovirus Type 11 Infection

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NEONATAL HEPATIC NECROSIS is fortunately rare.[1] Although a variety of enteroviruses have been recognized to infect fetuses and neonates,[2-4] the cause of most cases of fulminant neonatal hepatic necrosis is unknown.[1] Occasionally cytomegalovirus,[5] rubella[6] and echovirus types 3,[7] 6,[8] 9,[9] 11,[8,10,11] 14[12] and 19[13] have been directly associated with fatal hepatic necrosis during the neonatal period.

We report four cases of neonatal hepatic necrosis associated with echovirus type 11. These cases occurred sporadically during one year and each patient came from a different geographic area; thus at no time was an epidemic of echovirus type 11 suspected.

The perinatal histories were negative for viral illness as manifested by fever, vomiting, diarrhea or upper respiratory tract infections.

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Postmortem studies in case 4 were done by Zrino Bezmalinovic, MD.

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TABLE 1.—*Summary of Clinical Features and Results of Laboratory Investigations*

Data	*Case 1*	*Case 2*	*Case 3*	*Case 4*
Birth weight (grams)	3,856	3,359	3,154	2,765
Admission weight (grams)	3,000	2,934	3,000	2,540
Gestation (weeks)	37	38	38	38
First symptoms	Jaundice	Jaundice	Jaundice	Jaundice
Age	5 days	6 days	6 days	5 days
Bilirubin (mg/dl) (normal 1-12)	10.1	10.3	11.3	14.1
Platelet count (per cu mm)	39,000	46,000	10,000	31,000
Fibrinogen (mg/dl) (normal 200-300)	...	12	40	40
Fibrin-split products (μg/dl) (normal 0-3)	40	40	40	40
AST (IU) (normal 11-40)*	5,530	7,480	1,182	1,029
ALT (IU) (normal 11-40)†	1,370	2,040	227	197
AST/ALT ratio	4.0	3.6	5.2	5.2
Prothrombin time (sec)	45.0	33.5	28.9	28.6
Blood ammonia (μg/dl) (normal 11-35)	NP	158	108	NP
Viral cultures (Echovirus II)				
Liver	+	+	+	+
Lung	+	+	+	+
Parents	NP	NP	NP	NP

NP = not performed; + = positive.

*Aspartate aminotransferase, formerly SGOT.
†Alanine aminotransferase, formerly SGPT.

Reports of Cases

CASE 1. This infant was delivered by cesarean section to a 26-year-old primigravid woman. The mother was treated throughout her pregnancy with phenytoin sodium and phenobarbital for the control of a seizure disorder. Birth weight was 3,856 grams. The infant was discharged home at 3 days of age after an unremarkable hospital course.

The parents noted that the infant at 5 days of age was jaundiced, lethargic and had mottling of the lower extremities; he was readmitted to hospital. Examination showed that the abdomen was distended and tender with the liver edge palpable 8 cm below the right costal margin. Pertinent laboratory data are summarized in Table 1. Despite exchange transfusion with packed cells reconstituted with fresh frozen plasma, the infant's condition steadily deteriorated until his death the next day. The parents and a 15-month-old sibling were asymptomatic throughout the neonate's illness.

CASE 2. This infant was delivered by cesarean section because of cephalopelvic disproportion. The perinatal history was unremarkable except for a vaginal yeast infection two weeks before delivery. The Apgar score was listed as 9 at one and at five minutes. Birth weight was 3,359 grams. The infant had an unremarkable hospital course and was discharged home on the third day.

On the sixth day of life, a temperature of 39°C (102°F) developed and he was found to be jaundiced, with a serum bilirubin level of 10.7 mg per dl. A workup for sepsis was done, including a lumbar puncture, but proved negative. He became more lethargic and jaundiced and had some respiratory distress. The liver

was palpated 2 cm below the right costal margin. Laboratory data are summarized in Table 1.

Soon after admission, the infant had a generalized tonic-clonic seizure, following which his pupils became dilated and nonreactive to light. A bleeding diathesis then developed, characterized by an oozing from all puncture sites and a bloody endotracheal tube aspirate. Double-volume exchange transfusion with fresh whole blood was done to correct the disseminated intravascular coagulation and to replenish some of the coagulation factors. The infant's clinical condition deteriorated, however, and he died 24 hours after admission.

CASE 3. This infant was the product of a normal spontaneous vaginal delivery to a 25-year-old gravida 2, para 1 woman. Antenatal history and perinatal history were unremarkable. The Apgar score was listed as 9 at both one and five minutes. Birth weight was 3,154 grams. The infant had an unremarkable course in the first four days of life.

On the fifth day he was observed to be jaundiced, with a serum bilirubin level of 11.3 mg per dl. On the sixth day the infant became irritable and was feeding poorly. He was then admitted to hospital where pertinent physical signs included lethargy and poor response to stimuli; the abdomen was distended and tender and the liver edge was palpable 4 cm below the right costal margin. Biochemistry findings are summarized in Table 1.

Soon after admission the infant's blood pressure suddenly rose, followed by the sudden onset of apnea and bradycardia with poor response to stimuli. At lumbar puncture the fluid was found to be grossly bloody. An exchange transfusion with fresh whole blood was carried out. A computerized tomographic scan done thereafter showed massive intraventricular and intracerebral hemorrhage. The infant's clinical condition deteriorated and he died shortly thereafter.

CASE 4. The child was a male infant born to a 20-year-old gravida 3, para 3 mother by repeat cesarean section. The maternal history was significant for epilepsy, well controlled by phenobarbital therapy. Ten days before the birth premature labor occurred, felt to be due to asymptomatic bacteremia. Management included administration of ampicillin and parenteral terbutaline sulfate tocolysis. Oral administration of terbutaline was continued until term. Birth weight was 2,765 grams. Apgar score was listed as 9 and 10 at one and five minutes, respectively. The course in the nursery was unremarkable.

On day 5, while at home, the child was noted to feed poorly at the breast and to be lethargic and jaundiced.

The infant was admitted to hospital. Findings on general examination were remarkable only for icterus; the liver was palpable 1 cm below the right costal margin. Hematologic and biochemical studies showed a severe hepatitis with disseminated intravascular coagulation (Table 1).

Fresh frozen plasma and platelets were administered and an exchange transfusion with whole blood carried out. Despite these efforts, the disseminated intravascular coagulation progressed and evidence of hemorrhage emerged, progressing to circulatory collapse and death.

Determination of creatine kinase and serum aldolase levels was not done. Neither viral cultures nor titers from cord blood or parents were available. Viral cultures were done at postmortem examination on specimens from the liver and lungs and were positive for echovirus type 11 in all four cases.

Virology Studies

Specimens were taken from the lungs and liver at postmortem examination while the organs were in situ and before opening the bowel. The specimens were inoculated into human fetal diploid lung and primary monkey kidney tissue, which was incubated for 14 days. A daily check for cytopathic effect of cells was undertaken. From this cytopathic effect, a diagnosis of enterovirus was made and the culture was subpassaged to increase the viral concentration. Then, using the tube neutralization test (the Lim and Benyesh-Melnick schema[14]) the subspecies was identified. The identification was done at the Fresno County Laboratory using the standard method of the California State Health Department. Echovirus type 11 was isolated from the liver and lungs in all four cases that were evaluated.

Discussion

The enteric cytopathic human orphan (ECHO) group of enteroviruses is known to be capable of producing a wide spectrum of human diseases, including asymptomatic infection.[15,16] The infection occurs primarily in children and in young adults. The incubation ranges from 2 to 20 days, but is usually 5 to 10 days.[15] The most common symptoms are fever, headache, nausea and vomiting, sore throat, rhinitis, myalgia, rash and a cough accompanied by chest pain. These symptoms may reflect aseptic meningitis, carditis, encephalitis, gastroenteritis or pleurodynia. A familial incidence is common and there is a tendency for the condition to relapse or run a biphasic course. Infections due to echoviruses are seldom associated with serious residual effects.[15]

There are scant data implicating echoviruses in liver disease. Mild disturbances in liver function or hepatomegaly (or both) have occasionally been noted during outbreaks of echoviruses 1, 4, 6, 7, 8, 9 and 12.[17] Isolated cases of fulminant neonatal hepatic necrosis associated with echoviruses 3, 6, 9, 14 and 19 have been reported.[7,13] These reports described an illness with a rapid, fatal course of three to four days. Necropsy findings showed severe liver parenchyma loss but an intact reticular network, a surviving collar of hepatocytes around the portal areas and minimal mononuclear cell infiltration. Rarely, giant cells, iron deposition or calcification was noted. The destroyed hepatocytes were replaced by a pool of blood—mostly erythrocytes.

The cases described in this report are interesting because of the findings that appear peculiar to echovirus type 11 infection. The identification of echovirus type

11 at postmortem studies of specimens from the liver and lungs of all four infants is strong evidence that this virus represents the causal agent.[18] There was no evidence of coincidental infection or contamination. All the cases had features suggestive of disseminated intravascular coagulation, which could be a nonspecific phenomenon of severe acute hepatic failure. All the infants, however, also showed a unique and constant elevation of serum aspartate aminotransferase (AST, formerly SGOT)-to-serum alanine aminotransferase (ALT, formerly SGPT) ratio between 3.6 and 5.2. The AST-to-ALT ratio has been investigated as a diagnostic tool in many forms of liver diseases. Cohen and Kaplan[19] in a recent report concluded that a ratio of greater than 2 was highly suggestive of alcoholic hepatitis and cirrhosis. In only 4 percent of their patients with viral hepatitis was the ratio higher than 2. The highest ratio in viral hepatitis was marginally greater than 2. They also noted that in alcoholic liver disease, the serum ALT level was less than 300 IU in 98 percent of patients; thus, the increased ratio was accounted for by a disproportionate elevation of AST. In our patients, despite an AST-to-ALT ratio of 3.6 to 5.2, the serum ALT values ranged from 197 to 2,040 with a mean of 1,150 IU. The AST and ALT determinations were done on the same blood specimen and they were measured in the hospital chemistry laboratory on the DuPont ACA.[20,21] Where serial aminotransferase determinations were available, the ratio of every set was noted and every patient maintained a constant ratio of AST-to-ALT that was unique to that given infant (see Table 1 and Figure 1).

The high AST-to-ALT ratio in fulminant hepatic necrosis may be explained by the fact that in a normal liver, the *liver* AST-to-ALT ratio is 3.2,[22] and the serum ratio of 3.6 to 5.2 merely reflects an acute massive hepatic release of these enzymes. One doubts whether this is a specific feature of echoviral hepatitis.

In a recent report[23] of an echovirus type 11 epidemic in Japan affecting 102 patients, the authors noted that echovirus type 11 infections were less serious in neonates as compared with children of an older age. They also reported no remarkable gastrointestinal symptoms in any of their 42 neonates infected with echovirus type 11. A British study[24] of an outbreak of echovirus in a

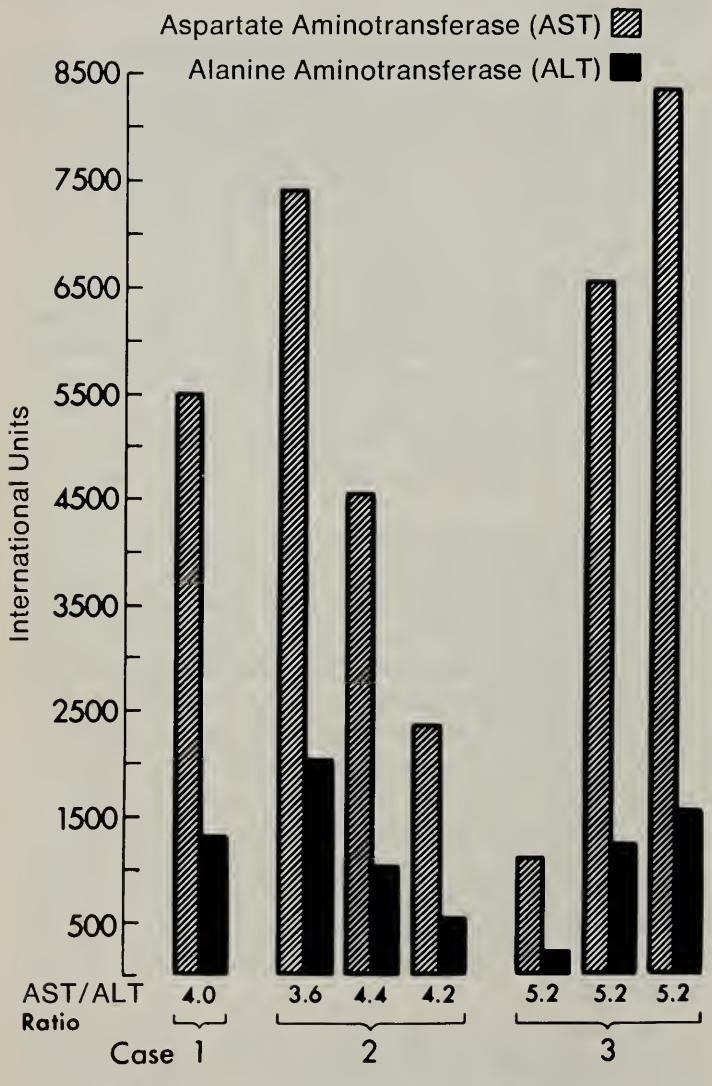

Figure 1.—The AST/ALT ratios of cases 1 through 3.

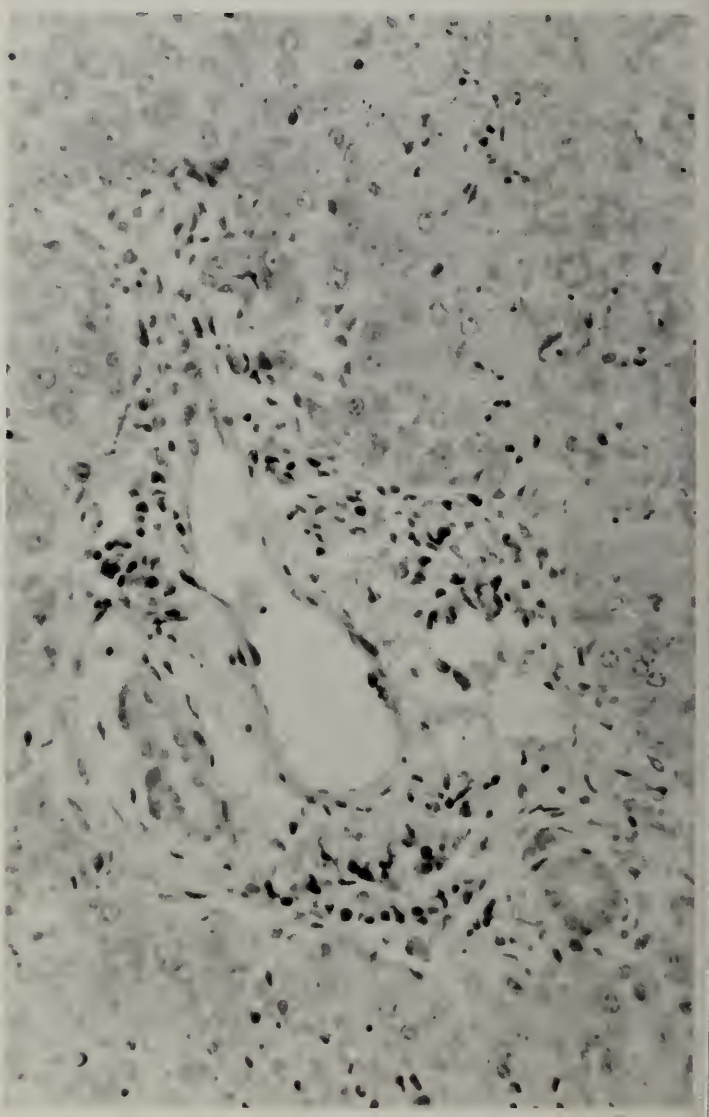

Figure 2.—Postmortem histologic examination of specimen of liver from case 4 showing massive hepatic necrosis with some intact periportal hepatocytes. Pronounced sinusoidal congestion is present in the necrotic areas. The portal triad is unremarkable. (Hematoxylin and eosin stain, reduced from magnification × 66.)

neonatal unit from which 9 to 24 became infected reports three infant deaths. In the three fatal cases there were renal and gastrointestinal lesions but no histologic abnormality in the liver. Six other patients, all of whom recovered, had predominantly an aseptic meningitis with apneic attacks or appeared "off color." All other fatal cases of echovirus type 11 infection reported in neonates have been due to disseminated intravascular coagulation. In each of these cases, the infants presented with a rapidly developing septicemic condition and died within 24 hours after the appearance of symptoms.[25,26]

This report expands the recently reported association between echovirus type 11 and fulminant neonatal hepatic necrosis.[8,10,11] Massive hepatic failure with extensive hemorrhage due to hepatic disease and disseminated intravascular coagulation have been the predominant clinical features in the previous six cases of echovirus type 11 fulminant neonatal necrosis. Previous isolated reports of neonatal hepatic necrosis have involved echoviruses 3, 9, 11, 14 and 19 and they describe a similar clinical picture. Liver histology in our infants showed almost complete necrosis of hepatocytes, with a collar of surviving hepatocytes around the portal tracts. These portal tracts and the hepatic lobular architecture appeared essentially intact. No hemosiderosis, calcium or giant cells were noted; no inflammatory infiltrate was evident, but there was extensive hemorrhage into the liver tissue (Figure 2).

The clinical course of our infants and the subsequent postmortem pathology appear similar to the five cases of neonatal hepatic necrosis described by Ruebner and colleagues,[1] except for the absence of hemosiderin deposition and hepatocytic giant cells in our cases. No cause was identified in the report of Ruebner and associates and most of these infants had massive adrenal hemorrhage as was encountered in our series. In both series, the infants were not premature and there was a rapid, fatal course reflecting disseminated intravascular coagulation, profound hemorrhagic diathesis, hypoglycemia and encephalopathy but only moderate serum bilirubin elevation. It is possible that the echovirus type 11 was the cause in both series or, more probably, neonates' livers have a limited response to severe damage regardless of the origin.

The epidemiology of the infection in our cases is obscure. The patients became ill on the fifth or sixth day of life, thus they could have acquired their infection either in utero[11,27] or after birth. No sources of contact for infection were identified when sought and the cases occurred over a wide geographic area and at a scattered time interval, thus eliminating the likelihood of an epidemic. The cardinal pathologic findings, apart from those already described in the liver, were disseminated intravascular coagulation and extensive adrenal hemorrhage.

Thus, in the light of our findings, echovirus type 11 expands the growing list of viral agents capable of causing fulminant hepatic necrosis. Severe echovirus infections appear to occur mostly in neonates and infants. The same viruses produce a much milder, self-limiting disease in older children and adults and are more likely to affect the respiratory and neurological systems in the older age groups.

A possible explanation for this is that transplacental passage of neutralizing echovirus type 11 antibody does not occur if the maternal infection occurs in the immediate antenatal period. Decreased immune response in a newborn would aggravate this unprotected state, thus predisposing to an overwhelming viremia. Recently, Modlin and associates[11,28] have shown that any passive immunity acquired from the mother prevents severe neonatal systemic echovirus disease. However, they showed that this does not prevent mucosal infection of the respiratory or gastrointestinal tract. Hence we conclude that infants of mothers with perinatal echovirus type 11 infection should be closely observed for the occurrence of liver disease. This would be especially important when the maternal infection occurs immediately antepartum.

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Imported South African Tick Typhus

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INTERNATIONAL TRAVEL is common today. Modern transportation enables persons harboring infections to travel to regions where a particular illness is rare or absent, and physicians are unfamiliar with the disease picture. We report here two cases of San Diego patients who had contracted South African tick typhus.

Reports of Cases

CASE 1. A 47-year-old physician was seen on January 27, 1981, with a self-diagnosis of South African tick typhus. On January 10 the patient, his wife and daughter had returned from a three-week safari in South Africa.

During the stay in Africa, each took chloroquine weekly and doxycycline hyclate, 100 mg, daily. The latter was discontinued two or three days before departure. Much of the time in South Africa was spent in the bush, including walking through tall grasses on a photographic safari in Zululand during the last part of the trip. On the day of his return to the United States, he removed an engorged tick from the tip of his penis. Although he did not recall removing any other ticks during his stay in South Africa, two days later he noted a lesion in the left inguinal region that had the features of a tick bite. On January 16 he noted lymphadenopathy, cough, subjective fever and increasing shortness of breath; he nevertheless was well enough to ski that week with his family. On January 20 he had fever (38° to 39°C [101° to 102°F]) and shaking chills, tachycardia, headache and myalgia. These symptoms persisted and on January 26 he first noted a diffuse maculopapular rash, most striking on the trunk, and diagnosed his illness as South African tick typhus. He then sought medical advice. Treatment with tetracycline, 1 gram a day, was begun. Within 24 hours he was afebrile and symptomatically much improved, though the rash persisted; he now noted arthralgia, particularly in the small joints of the hands.

On physical examination he appeared neither acutely nor chronically ill. He was afebrile and had a blood pressure within the normal range; the pulse rate was 100 beats per minute and regular. Pertinent abnormal physical findings were limited to the skin and lymph nodes. There was a diffuse nonconfluent maculopapular rash most striking over the trunk, but also present on the face, arms and legs (Figure 1). The rash was not petechial and blanched readily on pressure. There was no rash on the palms or soles. A nontender 8-mm black eschar surrounded by a 10- to 12-mm area of erythema and desquamation was present in the left groin (Figure 2). Adenopathy was limited to a single, 1-mm tender inguinal node directly above the eschar.

Laboratory studies disclosed the following values: hemoglobin, 15.9 grams per dl; hematocrit, 46.1 percent; leukocyte count, 4,300 per μl, with 56 percent segmented neutrophils, 14 percent band forms, 25 percent lymphocytes and 4 percent mononuclear cells. The platelet count was normal (262,000 per μl), but fibrinogen levels were elevated (296 mg per dl) and a thrombo-Wilcox test for fibrin-split products was positive (1:5 and 1:20).

The tick was identified by Dr Robert N. Philip at the Rocky Mountain Laboratory in Montana as a larva belonging to the genus *Aponomma,* species undetermined. Serologic tests carried out at the Centers for Disease Control showed a rise in indirect fluorescent antibody titers to *Rickettsia conorii* from 1:16 on January 26 to 1:256 on February 18. Antibody to Rocky Mountain spotted fever antigen also measured by indirect fluorescent antibody test showed a rise in titer from 1:32 to 1:256.

Four days after leaving South Africa, the patient's

Figure 1.—Rash on the trunk of patient in case 1.

Refer to: Barrett-Connor E, Ginsberg MM: Imported South African tick typhus. West J Med 1983 Feb; 138:264-266.

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Submitted, revised, February 24, 1982.

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wife noted upper respiratory symptoms, subjective fever and two eschars similar to the patient's lesion, one on the chest and one on the buttocks (Figure 3). She had no chills or rash. In addition to the 100 mg daily of doxycycline prophylaxis while in Africa, she had taken a cephalosporin by mouth for ten days after returning to the United States "because she thought she was getting a cold." Serologic studies on the patient's wife showed an indirect fluorescent antibody titer of 1:128 on both January 27 and February 18 to *R conorii,* and a titer of 1:128 on January 27 and 1:256 on February 18 to Rocky Mountain spotted fever antigen.

The patient's daughter remained well except for a cold after returning to the United States. She was taking 250 mg of tetracycline daily for acne control, and had taken 100 mg of doxycycline daily as diarrhea prophylaxis in Africa. She was not studied serologically.

CASE 2. A 57-year-old physician traveled through South Africa from July 15 to July 28, 1977. During his stay he made several trips to the bush and was aware of tick bites. On August 10 he noted the onset of severe malaise accompanied by a mild headache, fever and lymphadenopathy. A papular rash was observed on one hand and one leg distal to bite sites. The rash became vesicular and ultimately crusted. A clinical diagnosis of tick typhus was made, he was treated with tetracycline and recovery was uneventful. Indirect fluorescent tests for antibody to Rocky Mountain spotted fever antigen, carried out in the California State Health Services Laboratory, showed a rise in titer from less than 1:8 on August 4 to 1:1,024 on August 18. Serologic tests for *R conorii* were unavailable in 1977.

Discussion

Boutonneuse fever, a tick-borne typhus with *R conorii* as its agent, occurs throughout the African continent, in European and Middle Eastern areas adjacent to the Mediterranean, Black and Caspian Seas, and in India. It is a potentially important disease of travelers because attractive places and infected Ixodidae tick vectors are both found in these areas. Boutonneuse fever in tourists has been reported in the Netherlands, Germany and Switzerland.[1] These two cases serve as a reminder that the disease is also occasionally imported into the United States.

African tick typhus is a mild to moderately severe illness with a usual incubation period of five to seven days. In a typical case, a patient has fever for several days to two weeks, an initial lesion called a tache noire and a generalized maculopapular erythematous rash that appears on about the fifth day and often involves the palms and soles.[2] The tache noire at the site of tick attachment typically is seen on parts of the body

Figure 2.—Eschar on groin of patient in case 1.

Figure 3.—(top and bottom) Eschars on trunk of wife of patient in case 1.

covered by clothing, resembles a cigarette burn and is often accompanied by regional lymphadenitis. Malaise, headache and tachycardia are characteristic but nonspecific findings. Patients usually become afebrile within two to three days of taking tetracycline. Death is rare. Diagnosis is confirmed by seroconversion to *R conorii* antigen, or—with compatible exposure history and clinical manifestations—to the closely related antigen of Rocky Mountain spotted fever.

The first patient and his family are of additional interest in view of the antibiotic history and its apparent effect on the course of infection. The patient, his wife and daughter all took a tetracycline with sustained blood concentrations until two to three days before leaving Africa. This may have been responsible for the delayed onset of illness in the first patient and could have suppressed the infection in his wife, who had two eschars but no rash or seroconversion. It is also possible that infection in the daughter was prevented by her continuous use of low-dose tetracycline for control of acne. Others have shown that a single dose of doxycycline cures epidemic typhus *(Rickettsia prowazekii)*[3,4] and that a weekly 200-mg dose continued for six weeks after exposure prevents scrub typhus *(Rickettsia tsutsugamushi).*[5] Chemoprophylaxis of tick typhus has not been studied in man, but studies of guinea pigs infected with *Rickettsia rickettsii* suggest that the efficacy of a single dose of oxytetracycline depends on both the inoculum of rickettsiae and the timing of drug administration.[6]

Tetracylines stop rickettsiae from growing but the final eradication probably depends on a patient's immune responses. Early in the infection, rickettsiae grow equally well in macrophages and endothelial cells; antibody-coated rickettsiae can grow in endothelial cells but are rapidly destroyed in macrophages. Recovery from tick typhus therefore depends on the diversion of rickettsiae from endothelial cells—where they multiply and cause vasculitis—to macrophages, where they are destroyed.

Abnormalities of the coagulation system, most typically thrombocytopenia and disseminated intravascular coagulation,[7-12] have been reported in patients who have Rocky Mountain spotted fever. In the first case reported here, thrombocytopenia was not present, but hyperfibrinogenemia and an increased amount of fibrinogen degradation products were present. Because the platelet count was normal it is unlikely that the observed abnormalities were due to a consumption coagulopathy. It is more probable that the coagulation abnormalities were a consequence of vasculitis and the release of thromboplastic and fibrinolitic substances from damaged vessels. Studies of the coagulation and complement systems in rhesus monkeys with experimentally induced Rocky Mountain spotted fever also suggest that the hemostatic disturbances are a direct effect of the infectious vasculitis.[13]

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Antimuscle Antibody in Infantile Botulism

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INFANTILE BOTULISM, a disease resulting from intraintestinal toxin production by *Clostridium botulinum,* generally affects young infants. They present with constipation, slow feeding, hypotonia and diminished deep tendon reflexes.[1] A definitive diagnosis is established by the finding of *C botulinum* or its toxin in the feces of an affected infant. The disorder is treated with supportive measures, antitoxin having little or no clinical benefit, and survivors recover completely in one to six months.[2] We describe here a case of infantile botulism in which unusually prolonged duration of symptoms was associated with antiskeletal muscle antibody.

Report of a Case

A 4-month-old infant was brought to Childıens Hospital of Los Angeles with a five-day history of constipation, weak cry, fever and progressive hypotonia. On examination there were diffuse rales; bilateral ptosis; diminished suck, gag and deep tendon reflexes, and greatly diminished skeletal muscle tone. *C botulinum,* type A, and toxin were identified from stool specimens

Refer to: Newman LJ, Church JA, Landing BH, et al: Antimuscle antibody in infantile botulism. West J Med 1983 Feb; 138:266-267.

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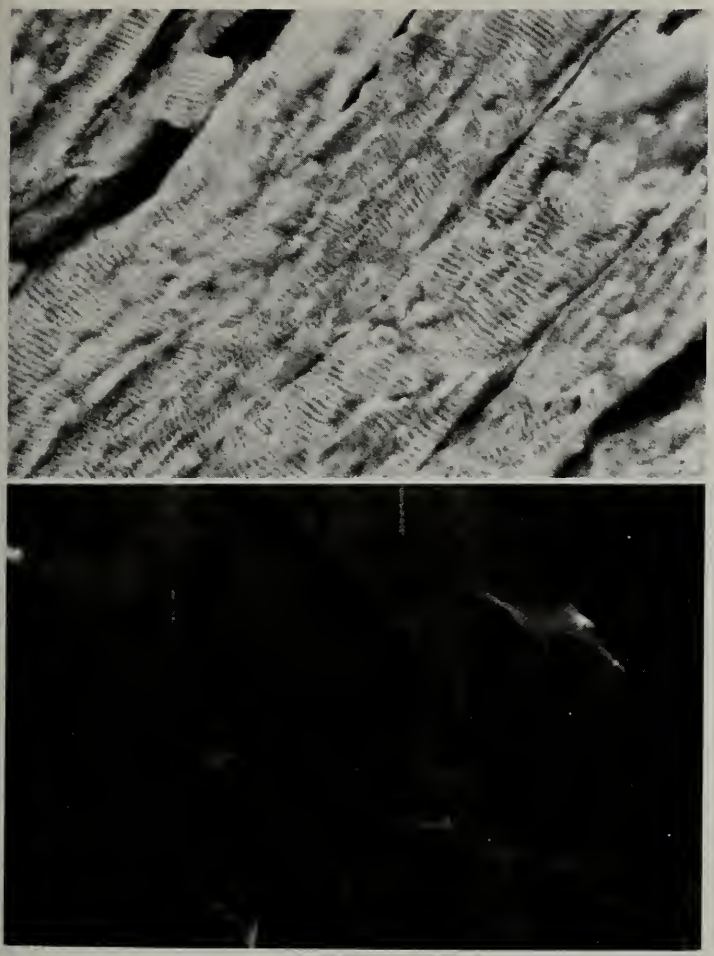

Figure 1.—Indirect immunofluorescence showing patient's immunoglobulin G fixation to normal skeletal muscle **(upper)** and lack of staining with normal serum **(below).**

and electromyography showed features of infantile botulism.[3]

Mechanical ventilation was instituted on the fourth hospital day and was required for seven months. *C botulinum* toxin was present in the stool for eight months, and clinical recovery was still incomplete ten months following presentation. Serum immunoglobulin levels, B- and T-lymphocyte number and in vitro mitogen responses were within normal limits. Serum analysis for antinuclear, anti-DNA and antiacetylcholine receptor antibodies was negative.

With an indirect immunofluorescent technique, the patient's serum was shown to contain immunoglobulin G antibody that produced selective staining of cross-striations of unfixed frozen sections of normal, blood type O skeletal muscle (Figure 1). This pattern has been reported as typical for myasthenia gravis.[4]

Three months after discontinuation of ventilatory support the patient's serum still contained this unique antimuscle antibody. Subsequently, the cases of two children with infantile botulism (one type A and one type B) were studied. Their clinical courses were of five weeks' and seven weeks' duration; their sera did not contain detectable antiskeletal muscle antibody.

Discussion

The finding of antiskeletal muscle antibody in the sera of patients with infantile botulism has not been reported previously. The prolonged hypotonia of our index patient and the clinical similarity of infantile botulism to myasthenia gravis prompted a search for antimuscle antibodies. Although assays for antiacetylcholine receptor antibodies were negative in this patient, antimuscle antibody was found. That this antibody is not a regular feature of infantile botulism is suggested by the negative antibody assays from two additional patients with classic infantile botulism. The persistence of botulinum toxin at the neuromuscular junction may have induced conformational changes in tissue antigens with subsequent autosensitization and the formation of autoantibodies. Whether this phenomenon was simply a consequence of prolonged toxin exposure or whether these antibodies contributed to this patient's prolonged clinical course is unclear.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgement before publication.

Shoulder Pain: Differential Diagnosis

TO THE EDITOR: The review by White in the October issue[1] outlines the general approach to the differential diagnosis of shoulder pain. Emphasis is placed on the description and treatment of local musculoskeletal conditions affecting the rotator cuff. Much less attention is given to a "variety of disorders" producing pain in the vicinity of the shoulder (cervical spine, neurologic dysfunction, neoplasia and others). Yet, a significant proportion of patients have neck-related pain as disclosed in a recent retrospective study of "shoulder pain" at our institution. Therefore, close attention to the evaluation of the cervical spine and the trapezial muscles, followed by a thorough examination of the rotator cuff, should yield diagnoses in 80 percent of cases. Having excluded these common conditions, one can rationally proceed in the evaluation of the intrinsic bone, joint or nerve processes (see Table 1 below).

TABLE 1.—*Differential Diagnosis of Shoulder Pain in 101 Patients Seen During 18 Months (Screened to Exclude Trauma Cases)*

Diagnoses	*Incidence (percent)*
Rotator cuff lesions	
Supraspinatus tendinitis/bursitis	51
Adhesive capsulitis	10
Reflex sympathetic dystrophy	1
Rotator cuff tears	1
Neck-related disease	
Trapezial muscle origin	17
Cervical radiculopathy	4
Biceps tendon lesions	
Tendinitis	2
Rupture	1
Acromioclavicular disease	
Osteoarthritis	1
Ligamentous strain	1
Partial separation	2
Scapulocostal syndrome	4
Glenohumeral disease	
Osteoarthritis	..
Rheumatoid arthritis	1
Arthralgia	1
Septic arthritis	..
Primary bone lesions	..
Miscellaneous	
Pectoralis strain	2
Polymyalgia rheumatica	1
Unknown or unclassifiable	2
TOTAL	102

Therapeutically, we disagree with the author's recommendation of immobilization of a painful shoulder for several days before initiating physical therapy (pendulum exercises). This places a subset of patients (perhaps as many as 25 percent) with acute supraspinatus tendinitis/bursitis at risk for adhesive capsulitis developing. This is especially true of a patient with a low pain threshold. We would strongly urge early corticosteroid injection and subsequent daily pendulum exercises for moderately severe to severe rotator cuff tendinitis/bursitis.

A prospective study of the efficacy of physical therapy, oral administration of phenylbutazone and local injection of corticosteroid in the treatment of supraspinatus tendinitis/bursitis is currently underway at The Oregon Health Sciences University.

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1. White RH: Shoulder pain (Topics in Primary Care Medicine). West J Med 1982 Oct; 137:340-345

* * *

TO THE EDITOR: I read Dr Richard White's October article on shoulder pain[1] with interest, and agree that in most patients "neurological" causes of pain in or about the shoulder can be suspected on the basis of symptoms and physical findings. I would like to remind the readers of *WJM* of a neurological syndrome that is often confused with musculoskeletal causes of shoulder pain by primary care physicians, especially early in its course.

Acute brachial neuritis, also known as brachial plexus neuropathy or neuralgic amyotrophy,[2] usually affects healthy young or middle-aged men. The typical patient first notes sudden, intense, unilateral shoulder

pain, most often described as "sharp," "stabbing," "aching" or "gnawing." This pain is not increased by Valsalva maneuver but is often exacerbated by motion of the shoulder. About a third of patients complain of paresthesias in the affected extremity. The pain lasts two or three weeks, during which the patient invariably seeks medical attention; as the pain improves, it is replaced by patchy weakness and atrophy of muscles innervated by the brachial plexus (most often the upper roots). The degree of atrophy and weakness is often profound and exceeds that seen in cervical radiculopathies.

Recovery of motor function is generally satisfactory but may take many months or years. The cause of brachial plexus neuropathy is not known; its occurrence following the administration of foreign sera or vaccines has led to speculation about an immune-mediated pathogenesis. There is no known effective treatment except physical therapy where indicated to prevent the consequences of prolonged joint immobility.

Failure to recognize the syndrome can lead to unnecessary cervical myelography or other invasive procedures, and incorrect diagnoses ranging from musculoskeletal conditions to motor neuron disease.

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To the Editor: White's nice review of common shoulder pain syndromes appropriately stresses the basic principles of accurate diagnosis and conservative treatment directed at early mobilization of the joint.[1] I believe a word of caution is warranted concerning his advice to treat "acutely inflamed shoulders" with injections of steroids. The author lists septic arthritis in his differential diagnosis of shoulder pain, but does not discuss this relatively uncommon condition. Infection of the shoulder may also involve the subdeltoid bursa. It occurs usually in patients with chronic illness or previous hospital admission but can appear very much like acute bursitis or tendinitis.[2]

I therefore recommend an attempt at aspiration of an inflamed shoulder, including both subdeltoid bursa and shoulder joint. If any fluid is retrieved, Gram stain and culture are advisable, with at least the former preceding any steroid injection that may compromise diagnosis and treatment of occult shoulder infection.

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Separation of Hypereosinophilic Syndrome From Acute Lymphoblastic Leukemia With Reactive Eosinophilia

To the Editor: In your September 1982 issue, Bachhuber and co-workers[1] presented a case of acute lymphoblastic leukemia with reactive eosinophilia. Their discussion concerning the diagnosis becomes less clear when subsequent clinicopathologic data are presented in following this patient from his original presentation at The Oregon Health Sciences University in April 1980 to autopsy in November 1980 at Sacred Heart Hospital in Eugene, Oregon.

Before the death of the patient, signs of congestive heart failure developed with gated cardiac output studies showing global hypokinesia. The mechanism of death was a cardiac arrhythmia. Autopsy showed an endocardiomyopathy with pronounced endocardial thickening due to fibrosis with eosinophilic infiltration at the base. This process extended into the mitral and aortic valves. Mural thrombi were present in the right and left ventricles. Eosinophilic infiltration also involved the lungs, liver and spleen. The bone marrow showed an increase in cellularity associated with a moderate increase in mature appearing eosinophils.

The original bone marrow study at The Oregon Health Sciences University in mid-October showed the blasts to have myeloid differentiation in the biopsy, with questionable lymphoid differentiation in the touch preparation. There was no maturation arrest in any cell lines. Chomosome markers showed abnormal cytogenetics.

A diagnosis of acute lymphoblastic leukemia with reactive eosinophilia is inconsistent with the clinicopathological data.[2] The pathologic findings at autopsy were completely in keeping with the hypereosinophilic syndrome.[3] Chromosomal aneuploidy has been reported with the hypereosinophilic syndrome.[4] The patient's diagnosis is a collection of clinical findings and, therefore, should be labeled a syndrome rather than a disease.[5]

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* * *

Dr Fitchen Replies

To the Editor: Without knowledge of the bone marrow findings, the hypereosinophilic syndrome (HES) was obviously an important consideration in my analysis of this case and a possibility that weighed heavily in my

diagnostic deliberations. I ultimately excluded HES for the reasons stated in the discussion.

With the marrow findings in hand, HES is excluded by definition. In their classic review on the subject, Chusid and co-workers stipulated that there be no other demonstrable cause of eosinophilia if one is to make the "diagnosis" of HES. When the patient was first seen at Oregon Health Sciences University, the marrow was diagnostic of acute leukemia with 30 percent blast cells as well as an increase in eosinophils. The morphologic and histochemical characteristics of the blast cells were consistent with a lymphoid origin. One could argue that it is more typical in acute lymphoblastic leukemia (ALL) to find the bone marrow "packed" with blasts, but this certainly is not a prerequisite for the diagnosis. Of note in this regard is the fact that in 7 of the 15 reported cases of ALL associated with eosinophilia the initial bone marrow examination showed less than 50 percent blast cells (see reference 2, table 5 for references). Although karyotypic abnormalities have been found in patients with HES, this finding also supports the diagnosis of acute leukemia.

The reported absence of leukemic cells in the bone marrow at autopsy casts considerable doubt on the antemortem diagnosis. However, Dr Markwell was kind enough to forward the autopsy material to me and to my eye the postmortem marrow is hypercellular and contains a mixed infiltrate of eosinophils and abnormal mononuclear cells.

Drs Markwell and Wilson seem to be particularly impressed by the finding of endomyocardial fibrosis at autopsy and imply that this lesion could not have resulted from reactive eosinophilia. However, in their monograph on the eosinophil, Beeson and Bass cite numerous reports of endomyocardial fibrosis occurring in patients with eosinophilia secondary to parasitic infections, asthma, tropical eosinophilia, solid tumors and leukemia, as well as in patients with HES, and conclude "the clinical circumstances seem to provide indisputable evidence that high and prolonged eosinophilia from any cause can produce this unique kind of cardiac damage."[3] Furthermore, in the 15 reported cases of eosinophilia secondary to ALL,[2] 4 of the 5 patients in whom autopsies were done were found to have endomyocardial fibrosis at postmortem examination and the fifth had numerous infarcts and mural thrombi.

Shungaard and co-workers[4] have recently shed light on the mechanism by which eosinophils produce endocardial damage. They studied a patient with early endocardial damage and eosinophilia secondary to a highly anaplastic lung cancer. They found deposition of major basic protein (MBP), cytotoxic specific constituent of eosinophil granules, in areas of endocardial fibrosis but not in unaffected heart chambers. Delamination of endocardium from basement membranes was noted in areas of heavy MBP deposition. Moreover, treatment of cultured endothelial cells with MBP induced detachment of adherent monolayers from the culture dishes.

In summary, the postmortem findings in this case are nonspecific and could have resulted from eosinophilia of any cause. The comments of Drs Markwell and Wilson suggest that the intrepid CPC discussant, heart pounding with anticipation, should not breathe easy when the pathologist stands up and says "You got it right." Still, for the reasons stated, I think I did.

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Possible Therapy for Snoring

TO THE EDITOR: Snoring is a very disturbing disorder for which no adequate pharmacotherapy has been recommended. There have been numerous mechanical aids devised, but all of these seem to be rather uncomfortable.

Since protriptylene has been reported effective in sleep apnea, perhaps by improving airway coordination,[1] I have been prescribing a small dose of about 10 mg at bedtime to snoring patients whose spouses or families complained that the noise levels were unbearable. It is well known also that snoring is a frequent concomitant of obstructive sleep apnea.

Most families thus far have reported a diminution or cessation of snoring after protriptylene therapy was instituted. I have not done a double-blind study on this problem, but such a benign intervention appears worthy of further trials.

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Hospital Charges in Rural Utah

TO THE EDITOR: The expansion in the number of rural hospitals over the past 30 years has provided many rural communities with a financial challenge. Low "front end" costs for these hospitals, many in part subsidized by Hill-Burton funds, have been affected by advances in technology, changing physician practice patterns, increasing employee salaries, shifts in the demographic characteristics of the population served, and the costs associated with meeting governmental and accreditation standards.[1] Closure of marginally surviving rural hospitals has been suggested as a means of reducing health care costs.[2] However, given the substantial emotional

TABLE 1.—*Charges for Daily Semiprivate Room Rate in Each Hospital for Time Period Two Years Before Affiliation to Two Years After Affiliation**

Group & Hospital	−2 Year Dollars	−2 Year (percent)	−1 Year Dollars	−1 Year (percent)	+1 Year Dollars	+1 Year (percent)	+2 Year Dollars	+2 Year (percent)
A1	$86.00		$95.00	(10.5)	$135.00	(42.1)	$140.00	(3.7)
A2	67.00		85.00	(26.9)	140.00	(64.7)	140.00	(0.0)
B1	-NA-		75.00		90.00	(20.0)	115.00	(27.7)
B2	78.00	(20.0)	90.00	(15.4)	112.00	(24.4)	125.00	(11.6)
B3	68.00		74.00	(8.8)	86.00	(16.2)	103.00	(19.7)
C1	63.00		72.00	(14.3)	87.00	(20.8)	96.00	(10.3)
C2	64.00		72.00	(12.5)	92.00	(27.7)	105.00	(14.1)

*Groups A and B represent for-profit affiliation. Group C represents nonprofit affiliation. Percent increase from the preceding year is shown in parentheses.

and monetary investment in many of these hospitals, this is usually only considered as a "last resort."

One option for solving financial problems has been the shift in ownership or management of these hospitals from communities to regional or national nonprofit or for-profit corporations. Chain, for-profit hospitals may be less costly than nonprofit hospitals.[3] However, the study on which this observation was based may have over-sampled urban hospitals. To more clearly understand this phenomenon in rural areas, we evaluated the impact of a change in hospital ownership or administration upon hospital charges in rural Utah.

In the last seven years 19 of 25 rural hospitals in Utah have undergone hospital chain management or ownership affiliation. Of these, seven allowed us to review charge information for a period extending two years before to two years after affiliation. Each belonged to one of three groups: two for-profit chains and one nonprofit chain. Each is located in a rural community of 25,000 people or less and contains fewer than 80 beds. We collected charge information on a number of services, including semiprivate room rate, nursery room rate, electrocardiograms and complete blood counts. These services were chosen based upon the assumption that they did not vary as a function of either diagnosis or hospital case mix. To verify and supplement data collected at each hospital, records of the State Medicaid Management System were also reviewed.

Because of the small sample and short period of the review, we felt that substantial analysis of the data would not be meaningful. Assessment of the trend of charges is interesting, nonetheless. For example, Table 1 presents daily room charges during each year for each hospital. Charges increased substantially more in the year immediately following affiliation than they did in the year before. The magnitude of the marginal increase in percentage for the first affiliation year ranged from 1.4 percent to 37.8 percent, with an average marginal increase of 17.9 percent. A similar trend existed for nursery room rates. For the five hospitals for which these data are available, rates in four increased more in the year following affiliation than they did in the year before (range, 5 percent to 102 percent), with the average marginal increase being 33.6 percent.

Comparing the hospitals with respect to for-profit and nonprofit status, group C, the nonprofit corporation, had, as a rule, lower percentage increases upon affiliation. Group C also had lower total increases in charges over the first two years of affiliation than the other two for-profit corporations. For example, group A hospitals showed a 57.8 percent average increase in semiprivate room rates over the first two years of affiliation and group B showed a 39.8 percent increase. Group C hospitals, on the other hand, showed only a 28.5 percent average increase. However, group A hospitals did average lower percentage increases in nursery room rates (66.4 percent) than group B (93.1 percent) and group C (84.6 percent).

For the less costly services (such as electrocardiograms and complete blood counts) a pattern was seen with group A increases being larger than those for group B, which are larger than found in group C.

Small hospitals have several options in adapting to increasing financial burdens. They may increase charges on their own, pass an often unpopular bond issue, associate with other rural or urban hospitals, contract for the services provided, or close. Eliminating unprofitable services is possible. However, unless a hospital maintains modern equipment and the widest possible range of services, patients may opt for care in facilities that they perceive to be more modern.[1] Also, without modern facilities, hospitals often cannot attract physicians.[4] Although increased charges may reflect a "catch up" phenomenon necessary to attain financial solvency, given previously reported information on the potential cost-effectiveness of merging rural hospitals,[5] several questions remain unanswered: Is there a true need in each community for a hospital? Is the relationship among charge for service, services offered and overall cost of operation influenced by the nonprofit or for-profit nature of the affiliating corporation? What impact do such affiliations have on the overall cost of health

care? And finally, what impact upon quality of care and health status can be expected from such changes?

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Pneumothorax: A Complication of 'Skin Popping'

To the Editor: The hazards of subcutaneous drug abuse in the cervicothoracic region have not been well documented in the recent literature. We wish to report a case of direct drug injection into the lateral thorax, resulting in a pneumothorax.

Report of a Case

A 29-year-old woman with a history of chronic intravenous and subcutaneous drug abuse was admitted with a chief complaint of severe right-sided pleuritic chest pain. The onset of her symptom began after a mixture of methylphenidate hydrochloride (Ritalin) and codeine was injected into the lateral right side of her chest. She said that there was no "charge" from this "skin popping" attempt, but shortly thereafter chest pain developed on the right side, originating from the site of the injection and radiating anteriorly and posteriorly. She noted no other symptoms.

On physical examination, the patient was well developed and in no acute distress. She had multiple skin lesions secondary to her drug injections on all extremities and thorax that ranged in appearance from scarred and sclerotic to erythematous, abscessed lesions. Her most recent site of injection was located at approximately the fifth intercostal space, anterior axillary line. On auscultation there were decreased breath sounds on the right. The findings on the remainder of the examination were unremarkable.

An x-ray film of the chest showed a small right-sided pneumothorax (Figure 1). Another film two days later showed partial resolution of the pneumothorax. The patient's symptoms lessened and she was discharged with warnings regarding the dangers of continued drug injection.

Figure 1.—An x-ray study showing small pneumothorax **(arrow)** on right side of patient's chest.

Comment

Chronic intravenous and subcutaneous drug abuse often leads to the injection of drugs in more unusual and dangerous sites after the more commonly accessible sites become sclerosed and unavailable.[1] These other sites are the neck, supraclavicular region and the thorax. As in the case presented, the possibility of a pneumothorax should be considered in a patient who has recently injected drugs and presents with chest pain.

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Topics in Primary Care Medicine

Falls in the Elderly: A Clinical Approach

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"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems (such as dizziness, pruritus, insomnia, shoulder pain and urinary tract infections) encountered in primary care practice that generally do not fall into well-defined subspecialty areas and are rarely discussed thoroughly in medical school, house staff training, textbooks and journals. Often the pathophysiology is poorly understood and clinical trials to assess the effectiveness of diagnostic tests or therapies may be lacking. Nevertheless, these problems confront practitioners with practical management questions.

The articles in this series discuss new tests and therapies and suggest reasonable approaches even when definitive studies are not available. Each article has several general references for suggested further reading. We hope this series is of interest and we welcome comments, criticisms and suggestions.

—BERNARD LO, MD
STEPHEN J. McPHEE, MD
Series' Editors

The tendency to fall is a serious problem associated with aging. Both the incidence of falls and the severity of complications rise steadily with age. Accidents are the fifth leading cause of death in people older than 65, and falls constitute two thirds of these accidental deaths; 72 percent of deaths due to falls in the United States occur in the 10 percent of the population that is 65 or older. About a third of this age group living at home will fall each year, and about 1 in 40 of them will be admitted to hospital. Of those who were in hospital following a fall, only about half will be alive a year later. Repeated falls are a common reason for admission of previously independent elderly persons to long-term care institutions. Among elderly persons in institutions, 10 percent to 25 percent will have a serious fall each year.

This high morbidity and mortality might be reduced in several ways. The US Public Health Service has estimated that two thirds of deaths due to falls are potentially preventable. Identifying and eliminating environmental risks in homes or institutions may prevent those falls due primarily to environmental causes. Adequate medical evaluation and treatment for underlying medical conditions might prevent many other falls. Finally, many patients who have irreversible medical problems causing their falls could still benefit from learning adaptive behavior to minimize the number and severity of falls. This article will present a systematic approach for determining why an elderly person falls and for minimizing the chances of recurrence.

Causes of Falls

Table 1 lists the major causes of falls. Accidents are the most common cause of falls, accounting for 40 percent to 50 percent in most series. However, many falls attributed to accidents are really due to the interaction between increased susceptibility to accidents because of accumulated effects of age and environmental hazards. Older people have stiffer, less coordinated and more dangerous gaits than do younger people. Posture control, body-orienting reflexes, muscle strength and tone, and height of stepping all decrease with aging and impair ability to avoid a fall after one trips unexpectedly. Impairments of vision, hearing and memory, also associated with aging, tend to increase the number of trips and stumbles. In addition to the increased vulnerability of elderly people, avoidable environmental hazards are frequent. Elderly people who live at home usually face many hazards which can be ameliorated (Table 2). Similarly for the 5 percent of those who live in institutions, many correctable environmental factors have been associated with falls (Table 3).

Refer to: Rubenstein LZ: Falls in the elderly: A clinical approach (Topics in Primary Care Medicine). West J Med 1983 Feb;138:273-275.

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Syncope, or unexpected loss of consciousness, is an important cause of serious falls. There are two major causes of syncope: decreased cerebral blood flow and metabolic derangements. Cerebral blood flow can be decreased in many situations, including hypovolemia, autonomic insufficiency, venous pooling and cardiac dysfunctions (such as arrhythmias, heart block and aortic stenosis). Among the metabolic derangements leading to syncope are hypoglycemia, hypoxemia and acute acid base disturbances. A history of syncope is often difficult to obtain from the patient, who may not be able to recall losing consciousness, may attribute the fall to a trip or to a "drop attack" or may have an impaired memory or mental confusion. Thus, witnesses frequently provide key information.

Drop attacks are sudden unexpected falls without loss of consciousness or dizziness and usually involve a sudden flaccid weakness in the legs. Drop attacks are usually attributed to transient vertebrobasilar insufficiency. The leg weakness is transient but can persist for hours. Sometimes tone and strength can be restored more rapidly by pushing the feet against a solid object. Recent data suggest that drop attacks are substantially less common than early studies had indicated.

Orthostatic hypotension, defined as a drop of more than 20 mm of systolic blood pressure between lying and standing, is extremely common in elderly persons, occurring in 20 percent to 30 percent of those living at home. It can arise because of several factors, including hypovolemia, venous pooling, autonomic dysfunction (often related to diabetes or central nervous system damage), low cardiac output, parkinsonism and certain drugs (including sedative, antihypertensive and antidepressant medications). The orthostatic drop may be more pronounced upon arising in the morning since blood volume tends to decrease during the night. Although orthostatic hypotension is common, it causes relatively few falls. It is likely to induce dizziness and a search for a seat rather than an abrupt fall. Also, people tend to have the symptom chronically and to adjust to it.

Falls associated with dizziness, giddiness or vertigo are extremely common. The patient usually has symptoms that reflect another underlying cause for the fall, such as cardiac dysrhythmia, orthostatic hypotension or cerebrovascular disease. However, the vertigo from vestibular dysfunction or drugs can certainly cause falls.

Diseases of the central nervous system, such as dementia, cerebrovascular disease, parkinsonism, seizures or gait disorders are often associated with falls. Drugs, including alcohol, are a causal or contributory factor in many falls. Especially important are sedative, antihypertensive, antidepressant, diuretic, and hypoglycemic agents, as well as alcohol. Other causes for falls include anemia, hypothyroidism, unstable joints and severe osteoporosis with spontaneous fractures.

Determining the exact cause or causes is frequently difficult. Most older persons who fall, as well as those who do not fall, have more than one of the many age-related or medical conditions that predispose to falls.

TABLE 1.—*Major Causes of Falls in the Elderly*

- "Accidents"
- Syncope (sudden loss of consciousness)
- "Drop attacks" (sudden falls without loss of consciousness)
- Orthostatic hypotension
- Dizziness/vertigo
- Neurologic dysfunctions
- Drugs (especially sedative, antihypertensive, diuretic and hypoglycemic agents, as well as alcohol)

TABLE 2.—*Factors Associated With Falls at Home*

- Unstable furniture and appliances
- Creaky stairs with poor rails
- Throw rugs and frayed carpets
- Poor lighting
- Low beds and toilets
- Pets
- Objects on floor

TABLE 3.—*Factors Associated With Falls Among Elderly Persons in Institutions*

- Recent admission or transfer
- Daytime sedation
- Hazardous furniture
- Slick hard floors
- Unsupervised activities
- Reduced number of nurses

TABLE 4.—*Approaching the Patient Who Fell*

- Assess and treat injury
- Determine probable cause of fall
  - History
  - Physical examination
  - Laboratory and other tests (such as complete blood count, serum electrolyte studies, electrocardiograms, Holter monitor)
- Prevent recurrence
  - Treat underlying illness
  - Reduce environmental hazards (home assessment)
  - Teach adaptive behavior (for example, slow rising, gait training, cane or walker use, falling techniques, getting-up techniques)

Diagnostic Approach

Following stabilization of any acute problems brought on by the fall, such as head injury or fracture, the physician should undertake a careful diagnostic search for the underlying cause of the fall. A careful and well-directed history is the most important part of the diagnostic process for patients who have fallen. Obtaining a full report of the circumstances and symptoms of the fall is important, but often the patient has no or only a vague memory of it, and reports from witnesses may be the best that can be obtained. Terms like dizzy or giddy need to be defined clearly. There are several circumstances in the history that can point to a cause, including a sudden rise from a lying or sitting position (orthostatic hypotension), a trip or slip (gait disturbance or accidental fall), an unexplained drop attack without loss of consciousness (vertebrobasilar insufficiency) and looking up or sideways (arterial compression). Symptoms experienced near the time of

falling may also point to a cause: dizziness or giddiness (orthostatic hypotension, vestibular problem, hypoglycemia, drugs), palpitations (arrhythmia), incontinence or tongue biting (seizure), asymmetric weakness (stroke or transient ischemic attack), chest pain (myocardial infarction) or loss of consciousness (syncope). Also important to note are medications taken and existence of concomitant medical problems. (See Table 4.)

Physical examination can also point to causes for a fall and confirm or refute possible causes suggested by the history. Especially important to look for are orthostatic changes in pulse and blood pressure, arrhythmias, carotid bruits, nystagmus, focal neurologic signs, muscle weakness, joint deformities, unsafe footwear, visual loss, gait disturbances and occult blood in the stool. It is also frequently useful to attempt, under carefully monitored conditions, to reproduce the circumstances associated with the fall, such as positional changes, head turning, urination or carotid pressure.

The laboratory evaluation need not be extensive, but should include several tests in all patients in whom the cause is not obvious. Although the diagnostic yields of specific tests in evaluation of falls have not been well documented, several tests which can uncover etiologic factors are probably indicated. These include a complete blood count (to search for anemia or infection), serum chemistry determinations (for example, sodium, potassium, calcium, glucose and blood urea nitrogen values) and an electrocardiogram (to document arrhythmia or heart block). Thyroid function tests are also indicated if any suspicion of thyroid dysfunction exists.

Unfortunately, maneuvers or tests done at the time of the medical evaluation may not detect an intermittent problem that occurred at the actual time of the fall. In particular, orthostatic changes, arrhythmias, heart block, hypoglycemia or electrolyte disturbances may not be detected when the patient is examined. These tests may have to be repeated if the history or physical examination suggests an intermittent cause. An ambulatory cardiac (Holter) monitor is advisable when a transient arrhythmia is suspected or in the case of otherwise unexplained syncope. The likelihood of finding suggestive abnormalities on Holter monitoring in older persons who fall is particularly high. In one small series, 32 percent had arrhythmias documented on Holter monitoring which were felt to be responsible for falls. Of these, only a sixth had evidence of the arrhythmia on the initial resting electrocardiogram. Because the prevalence of transient arrhythmias is high in the asymptomatic elderly population it is often unclear whether an abnormality detected on the monitor caused the fall, unless corresponding symptoms were noted during the monitoring process.

Therapy and Prevention

Once the cause for a fall is determined, therapy can be appropriately instituted. For example, cardiac dysrhythmias that have been clearly related to a fall should be treated with antiarrhythmics or a pacemaker, or both. Hypovolemia from hemorrhage needs treatment directed toward the bleeding site and toward restoring hemodynamic stability. More difficult is managing and preventing recurrent falls in patients who do not have easily reversible causes for the falls.

Patients with gait disturbances can often benefit from using a walker or cane or from gait training from a physical therapist. Special shoe modifications can often improve safety.

Patients with persistent orthostatic hypotension from autonomic dysfunction often benefit from sleeping in a bed with the head raised to minimize sudden drops in blood pressure on arising, from elastic stockings to minimize venous pooling in the legs and from instructions to rise slowly or to sit on the side of the bed for several minutes before standing up. Increasing circulating blood volume with additional dietary salt or mineralocorticoids may also be helpful if care is taken not to precipitate or worsen congestive heart failure or hypertension.

Persons subject to drop attacks from vertebrobasilar insufficiency associated with head motion may be helped by a cervical collar.

A careful search for and correction of other medical factors that contribute to falling (such as visual and hearing deficits) are essential. Where irreversible problems exist, residual limitations should be explained and coping methods developed. For example, patients with neurologic defects often derive great benefit from assessment and specific therapy from rehabilitation specialists such as occupational and physical therapists.

A home assessment by a visiting nurse or other trained health-care worker can suggest appropriate modifications of the home environment. Such modifications include elimination of hazards (loose or frayed rugs, trailing electric cords, unstable furniture) and environmental improvements (improved lighting, grab rails in the bathroom, secure banisters, raised toilet seats, an alarm system). Such environmental modifications are probably useful in the homes of most elderly persons. Indirect data to support this practice come from institutional studies. Institutions that are specially designed to meet the needs and vulnerabilities of older persons have substantially lower accident rates than those designed without such special attention.

Since a third to two thirds of falls in elderly people are probably preventable with careful medical attention and environmental improvements, a vigorous systematic diagnostic, therapeutic and preventive evaluation is appropriate in all older patients. Any reduction in the fifth leading cause of death in the elderly will clearly have major impact.

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Health Care Delivery

Effects of Clinical Preceptorship on Career and Practice Site Choices

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To evaluate the effects of primary care preceptorships on the choices of career site and specialization, graduates of the University of Utah School of Medicine, 1972 through 1975, were questioned. Most practicing physicians who elected preceptorship training rated the experiences as valuable, but not important enough to be required. Physicians based their decisions for an urban practice on medical factors; rural areas were chosen more for personal reasons. In addition, data showed that the size of the respondents' hometowns was not associated with their choice in the size of their practice site nor their specialty. Respondents also reported that their medical school training was deficient in preparing them for the economic and psychosocial aspects of medical practice. Many Utah graduates are participating as clinical faculty or as preceptors for medical institutions and indicated that for their particular communities family physicians, obstetricians-gynecologists and pediatricians are still needed.

Since 1972 the University of Utah School of Medicine has participated in a federally funded primary care preceptorship program for medical students during their clinical years. Health Manpower Legislation (PL 92-157), passed in 1971, authorized support for programs that would give medical and osteopathic students preceptorship training with physicians in family practice, internal medicine or pediatrics. The major goals of the program are to remedy the geographic maldistribution of physicians and to reverse the trend toward subspecialization, thus helping to meet the need for primary care physicians in rural areas. By 1978 approximately $28 million had been awarded to 75 medical and osteopathic schools to support this program.[1]

The educational benefit of preceptorships has been well substantiated.[2,3] However, although it has been shown that physicians who participated in rural training programs were more likely to choose rural practice settings,[4] no evidence has been found to show that the preceptorship experience itself directly affects the choice of specialty.[2,5] It has been reported that participation in a clinical preceptorship is one of the characteristics associated with students selecting family practice as a specialty, as are being male and from a rural community.[1] Most of the studies regarding career choice and community site selection have been done on medical students' plans before actual completion of residency training and establishment of practice. The purpose of this study was to question practicing physicians to determine those factors that actually influenced their specialty and practice site selections.

Methods

The Primary Care Preceptorship Program at the University of Utah School of Medicine offers elective credit to students who during their clinical training (third and fourth years) spend a minimum of four continuous weeks with primary care physicians, that is, family physicians, pediatricians and general internists. Students are encouraged to take their families with them, and a few actually live with their preceptors. Both rural and urban sites are available. These clinical preceptorships in primary care provide students with an opportunity to perform those procedures in which they feel com-

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TABLE 1.—*A Summary of Available Data on the Respondent and Nonrespondent Populations*

	Respondents (N=133)		*Nonrespondents (N=128)*	
	Number	*Percent*	*Number*	*Percent*
Primary care specialists	53	39.8	49	38.3
Precepted	26	49.0	...	...
Primary care preceptorship	26	100.0	...	...
Other	...	...	...	...
Nonprimary care specialists	80	60.2	79	61.7
Precepted	58	72.5	...	...
Primary care preceptorship	35	60.0	...	...
Other	23	40.0	...	...
Men	129	97.0	121	95.0
Women	4	3.0	7	5.0
Married	118	88.7	...	...
Board certified	74	55.6	...	...
Urban practice	119	94.4	...	...
Rural practice	7	5.5	...	...
Urban hometown	85	69.1	...	...
Rural hometown	38	30.9	...	...
Preceptorships				
Yes	84	63.2	...	...
No	49	36.8	...	...

petent under the supervision of a practicing physician. Thus they both observe and acquire hands-on experience.

A questionnaire was developed and sent to all Utah graduates from between 1972 and 1975 for whom addresses were known. These years were chosen because most physicians graduating then would have completed their residencies and would now be in practice. All would have also had an opportunity to elect the clinical preceptorship option. Respondents were asked about their participation in the preceptorship program, the effect of the preceptorship experience on their choice of specialty and practice site, their opinions as to whether a preceptorship should be required, what, if anything, they felt was lacking in their medical preparation and what factors they felt influenced their selection of a community in which to practice.

Of the 272 questionnaires sent, 11 were returned as not deliverable by the post office. Of the 261 remaining questionnaires, 133 were returned, for a response rate of 51 percent. Responses were divided into a primary care group consisting of those physicians who are now practicing family medicine, pediatrics or general internal medicine and a nonprimary care group that included all the others. There was no significant difference in the response rates of primary care versus nonprimary care physicians (Table 1).

Statistical tests used for the data analyses were the x^2 test for independence with Yates' correction factor and the Fisher's exact test. Significance was determined at the .05 level.

Results

Sample Description

Of the 133 respondents, those actively practicing as primary care physicians represented 39.8 percent (53), with 60.2 percent (80) representing other specialties. From residency match information, 38.3 percent (49) of the nonrespondents pursued primary care specialties. Table 1 outlines the data available on both groups. Generally, those in the respondent group are men, married, board certified and in private practice, living in urban communities. Of the nonrespondents, 95 percent are men; additional information was unavailable.

Of the respondents, 63 percent (84) had participated in a preceptorship, most of whom (73 percent) took it for credit through the primary care preceptorship program. The other preceptorships mentioned were noncredited, individualized experiences taken on an ad hoc basis. (These experiences are usually arranged by each student and are so varied, and so few, that they were omitted from the analyses.)

Almost half of the respondents, 48 percent (64), are now serving as clinical faculty or as preceptors for medical schools, or both.

Specialty Choice

The data do not support the popular assumption that the size of a physician's hometown is a major influence on his or her choice of specialty. For our purposes, "rural" is a community of less than 10,000 population. Persons from rural areas chose almost equally the subspecialties of urology, radiology, pathology and psychiatry, as well as the primary care fields of family practice and internal medicine. There was no significant association between size of hometown and specialty selection ($x^2 = 30.37$, $P = > .05$).

Of the group who chose nonprimary care specialties, 58 (72.5 percent) also completed preceptorships; most (60 percent) also trained with primary care physicians. Only 49 percent (26) of the primary care group took a preceptorship; nevertheless, all (100 percent) were with primary care physicians. Most respondents (56, or 67 percent) who had taken a preceptorship felt that the training did influence their career goals and their eventual choice of a practice site. Only 22 (26 percent) of the entire precepting group felt no influence could be attributed to their preceptorship training. However, there was no consensus on whether a preceptorship should be required: 38 (45 percent) of those who did preceptorships, as opposed to 6 (12 percent) of those who did not, thought that a preceptorship should be a required experience. The most frequent reasons given for requiring it were to provide "real world" experience and to help choose a specialty. Many who felt a preceptorship should not be required did feel that the experience was valuable and should be strongly encouraged.

Rural Versus Urban Site Selection

It was interesting to contrast the physicians' reasons for choosing an urban as opposed to a rural community for their practices. "Urban" is defined as a community of larger than 10,000 population. Physicians cited medically related reasons for deciding on an urban

practice: they felt that larger communities had better medical facilities; they preferred to specialize, and, as urban practitioners, they would have access to subspecialty consultations. The broader entertainment and cultural opportunities in urban areas were mentioned as important, but not as frequently. On the other hand, physicians in smaller communities made their practice-site decisions more for personal-familial reasons: they liked the life in a small community and preferred to raise their families in one and the influence of the spouse was cited. Most respondents (73 percent) said if they had the choice they would choose the same practice site again.

There were only seven physicians currently practicing in rural communities. All of these physicians had taken a primary care preceptorship and were currently practicing in one of the primary care specialties. Most of the total precepting group did their training in urban communities (61 percent), yet 39 percent took their preceptorship in a rural community.

Much of the literature has indicated the strong influence the place of rearing has on the eventual choice of a practice site. Respondents' size of hometowns was compared with the size of the actual practice site. Most respondents (85) were from urban communities (69 percent). However, 38 (31 percent) indicated that they were raised in towns of less than 10,000 people. No relationship was found between urban or rural rearing and eventual practice site size (Fisher's exact test, $P = >.9$). Only two physicians who were reared in a rural site were currently practicing in a rural community, whereas 36 physicians whose hometowns were less than 10,000 population were practicing in urban locations. Five physicians raised in urban populations were currently practicing in a rural area.

Training Deficiencies

One of the most interesting responses coming from all specialties was the feeling that their training during medical school and residency had not prepared them for the business and psychosocial aspects of practicing medicine. For planning purposes, graduates were asked if additional physicians were needed in their geographic areas; family practitioners were most frequently mentioned, with obstetrician/gynecologists and pediatricians the second most needed. Additionally, it was found that respondents made career choices during their third year (33.1 percent) in medical school, their fourth year (20.3 percent) and as interns (20.3 percent). Other responses were as first-year students (4.5 percent), residents (8.3 percent) or at other times (12.8 percent). This is not surprising because to select a residency, most interview trips are made at the beginning of the fourth year; therefore, students must decide which programs to visit in order to plan their senior schedules.

Discussion

Our data agree with previous studies that show primary care physicians are more likely than other specialists to have had a primary care preceptorship experience during medical school. The difference, however, is not proportionately significant. Of the nonprimary care group 44 percent (35/80)—and of the primary care group 49 percent (26/53)—took a preceptorship with family physicians, pediatricians and internists. The data show that the preceptorship experience probably affects decisions on specialty and practice site selection regardless of career decisions: 67 percent of all respondents who had taken preceptorships said that the experience affected either their specialty choice or their decision about a practice location. Of the primary care physicians, 77 percent reported having been affected. This reinforcing mechanism may be very important when one considers that more than 50 percent of students recently entering the University of Utah School of Medicine expressed an interest in primary care.

Perhaps even more important is the finding that a greater percentage of students have decided by their fourth year on a specialty, especially in view of the fact that most primary care preceptorships take place during the fourth year. The influence of a preceptorship on career choices might be greater if primary care preceptorships were available earlier, that is, as part of the third year or during the preclinical years.

Nonprimary care specialists who participated in primary care preceptorships also responded favorably to its effects. The preceptorship was viewed as having helped them decide among a wide range of career choices.

About 44 percent of those who completed preceptorships felt that the experience was valuable enough that it should be a required part of medical student training, with the others highly recommending it. As far as alleviating the geographic maldistribution of physicians, a minor impact is being made. Of those seven respondents currently practicing in a rural area, all had taken primary care preceptorships and all were practicing primary care.

Conclusions

Preceptorship experiences that give students hands-on clinical opportunities appear to have a reinforcing effect on predisposed career and practice site preferences. The larger numbers of entering first-year students who are expressing an interest in family medicine might be further encouraged to choose a career in primary care if these preceptorships were available earlier in the training process. Although the major purpose of this study was to determine the effects of the primary care preceptorship experiences, additional data offered other indications concerning what influenced physicians' careers and eventual practice sites. Major conclusions are as follows:

- Respondents who had participated in a preceptorship felt the experience influenced both their specialty choices and their choices of practice site.
- Although only seven respondents were practicing

in a rural community, all were primary care physicians and all had taken a primary care preceptorship.

- There was no association between size of hometown and specialty selection.
- There was no association between the size of hometown and the size of practice site selected (urban versus rural).
- Physicians selecting smaller communities for their practices gave personal-familial reasons for selecting a small community, whereas medically related reasons were important in urban site selections.
- Deficiencies in respondents' training were cited as a lack of business and psychosocial preparation for the practice of medicine.
- There is still a perceived need for family physicians, obstetricians/gynecologists and pediatricians in both urban and rural populations.

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Medical Practice Questions

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Intraarterial Carmustine (BCNU) Chemotherapy

QUESTION:

Is the use of intraarterial carmustine (BCNU) *chemotherapy for the treatment of malignant brain tumors an acceptable and established procedure falling within the scope of clinical practice, or should it be considered an investigational procedure to be carried out in a research facility with protocol?*

OPINION:

In the opinion of the Scientific Advisory Panels on Internal Medicine and on Neurosurgery, intraarterial carmustine (BCNU) chemotherapy for the treatment of malignant brain tumors should be considered investigational until its safety and efficacy have been demonstrated. Though this method of treatment appears to hold some promise, there is no evidence that the use of intraarterial carmustine (BCNU) chemotherapy is superior to conventional intravenous administration. Moreover, the known systemic toxic effects, both hematologic and nonhematologic, are significant hazards.

Controlled studies are required to determine if the added morbidity of arterial puncture and the increased risk of local drug toxicity (for example, retinal injury) are outweighed by a gain in therapeutic effect.

The procedure, therefore, remains the subject of investigation and should be used under appropriate research protocol in medical centers where rigorous scientific analysis and comparison with other modalities can be accomplished.

Training Physician Assistants for the Pacific Northwest

The MEDEX Northwest Ten-Year Experience

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The student characteristics and employment status of physician assistants trained at MEDEX Northwest in Seattle between 1969 and 1979 were surveyed. There were 201 graduates and an attrition rate of 11.1 percent. Of 142 respondents, 88.7 percent were currently employed as physician assistants or nurse practitioners. Most (77.5 percent) were employed by their teaching preceptors following graduation. A majority (55.6 percent) were working in public or nonprofit private sector facilities.

In all, 70 percent were practicing in Washington state, 75 percent were in family practice and 62 percent were working in communities of less than 50,000 population. These results compare favorably with rural and primary care practice data for physician assistants and physicians nationally. An effective preceptorship and deployment system is proposed as an important reason for the results.

MEDEX* Northwest, a physician assistant (PA) training program, was founded in 1969 under the cosponsorship of the University of Washington and the Washington State Medical Association. Its goal has been the education and placement of primary care PA's in medically needy (especially rural) areas of the states of Washington, Alaska, Montana, Idaho and Oregon. Funded mainly by federal training grants, the program has utilized a one-year curriculum including three to six months of didactic course work at the University of Washington and 6 to 12 months of field preceptorship, where a majority of the graduates continue to practice. The background of the program is amply described elsewhere.[1-4]

Minimal qualifications for student entry are a high school education and at least two years of experience in a primary health care delivery role. Senior (400 level) college credit and a MEDEX PA certificate are awarded upon completing the year of study. A bachelor's degree can be earned with additional coursework, but is not mandatory. MEDEX graduates are fully eligible to take the PA national certifying examination and to register with individual states for PA practice.

*The name MEDEX is derived from the French words "MEDecin EXtension," meaning physician's extension.

Rationale

The purpose of the survey was to describe and evaluate the student characteristics, professional status and employment distribution of PA's trained and graduated at MEDEX Northwest from 1969 to 1979. The basic question to be answered was whether or not the program's methods were resulting in substantial primary care and rural practice deployment among its graduates. The MEDEX curriculum is "competency-based," meaning that its content is derived from task analysis which leads to objectives that specify the knowledge and skills necessary to carry out defined tasks. The MEDEX training model has been noted for its emphasis on selecting students with substantial prior health care

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ABBREVIATIONS USED IN TEXT

PA = physician assistant
NP = nurse practitioner
RN = registered nurse

experience, teaching practical skills and placing students in well-matched preceptorship sites that are intended to provide full-time jobs after graduation. The current 12-month training period is significantly shorter than the norm of 24 months for most PA programs.

Methods

Demographic and prior training information was obtained from MEDEX Northwest files on all 226 PA students accepted between 1969 and 1978. A nine-page direct mail questionnaire survey was done from January to May 1980, seeking responses from all 201 graduates of the program from 1970 to 1979. Data were sought on employment history, board certification status, geographic location and characteristics of the supervising physician or physicians. Questionnaire information was obtained from 142 of 201 graduates for a response rate of 71 percent.

Results

Student Body Profile and Attrition

Table 1 lists the number and percentage of students accepted and not graduated by various characteristics. Of 226 students accepted, 25 have not graduated, for an overall attrition rate of 11.1 percent. This has held relatively constant over the past ten years. Women have made up 24 percent of all students, with a pronounced increase from zero in the early years to about half in the late 1970s. A majority of these women have been registered nurses (RN's).

The differences in the proportions of Table 1 were tested using the normal approximation to the binomial distribution. The lower attrition rate for women (5.4 percent) versus men (12.8 percent) was not statistically significant ($\alpha = 0.14$). Of the 54 women accepted, 32 were registered nurses. All three of the women who failed to graduate were RN's.

Racial and ethnic minority students have comprised about 13 percent of all students accepted. This has held relatively constant over the years. The distribution has been 15 (50.0 percent) Hispanic, 8 (26.7 percent) black, 4 (13.3 percent) Asian and 3 (10.0 percent) Native American. The higher attrition rate for minority students (20.0 percent) versus nonminorities (9.7 percent) was not statistically significant ($\alpha = 0.09$).

Table 1 also lists the number and percentage of students accepted and not graduated by status as exmilitary corpsmen, RN's, and others as well as formal college education. Although excorpsmen have made up 65.5 percent of all students, their percentage has been decreasing substantially over the past six years to about a third in the late 1970s.

The attrition rate for excorpsmen was not significantly different from RN's ($\alpha = 0.28$). The attrition rate for students with less than or equal to two years of college preparation (15.5 percent) was significantly greater than that for those with more than two years (6.9 percent) ($\alpha = 0.05$). Of the 25 students who did not graduate, 14 failed and left for academic reasons and 11 left for personal reasons.

TABLE 1.—*MEDEX Northwest Physician Assistant Students (1969-78) by Sex, Minority Status, Former Training and College Education Versus Attrition*

Category	Number (Percent) Accepted (N = 226)	Number (Percent) Not Graduated [N = 25 (11.1%)]
Men	172 (76.1)	22 (12.8)
Women	54 (23.9)	3 (5.4)
Minorities	30 (13.3)	6 (20.0)
Nonminorities	196 (86.7)	19 (9.7)
Excorpsmen	148 (65.5)	20 (13.5)
Registered nurses	41 (18.1)	3 (11.5)
Other	37 (16.4)	2 (5.4)
≤2 Years college	110 (48.7)	17 (15.5)
>2 Years college	116 (51.3)	8 (6.9)

Source: MEDEX Northwest file data.

TABLE 2.—*Characteristics of Respondents and All Graduates*

Category	Respondents Number (Percent) (N = 142)	All Graduates Number (Percent) (N = 201)
Men	107 (75.4)	150 (74.6)
Women	25 (24.6)	51 (25.4)
Minorities	22 (15.5)	24 (11.9)
Excorpsmen	87 (61.3)	128 (63.7)

Characteristics of Respondents and Nonrespondents

Table 2 lists respondents to the questionnaire survey by sex, racial minority and excorpsman status, in comparison with all graduates. There was no significant difference between the group responding and the total population for these factors ($\alpha = 0.34$ to 0.88). The mean present age of male respondents was 37.3 years (SD = 6.8) and of females was 35.1 (SD = 6.3), with the combined age mean being 36.8 (SD = 6.8). The mean duration of years worked since graduation was 5.2 (SD = 3.1).

Employment

MEDEX graduates who are RN's have had the choice of becoming certified and registered as either a PA or nurse practitioner (NP). Of 142 respondents, 126 (88.7 percent) were currently employed as a PA or NP. Of these, 109 reported PA employment, 13 reported NP employment, and 4 reported both PA and NP. Of 41 RN's responding, the 13 represent 31.7 percent choosing to work as NP's instead of PA's.

Of those not employed as PA's or NP's, 12 listed their other employment pursuits. They included five unemployed, two nursing educators, one emergency medical technician instructor, one medical claims inspector, one medical receptionist, one self-employed and one physician. From MEDEX Northwest files, we

know that at least three graduates have gone on to medical school, for a rate of 1.5 percent.

Geographic Distribution

For 120 graduates employed as PA's or NP's, Table 3 describes distribution by state. Of note are the 70.0 percent working in Washington, especially the 40.0 percent in the western region where the training program is located.

Table 4 describes distribution by population of community where working. About 62 percent of MEDEX Northwest graduates were working in towns or cities of less than 50,000 population. A 1978 nationwide PA survey found 47 percent of all respondents in this category.[5] This difference is accounted for chiefly by the high percentage of MEDEX Northwest graduates in communities of under 10,000 population (about 41 percent) versus 25 percent of PA's nationwide.

Practice Organization

Table 5 describes the PA's employer's practice setting relative to tax status. Of those who gave an informed answer, a majority (55.6 percent) reported working in the public or nonprofit sector.

TABLE 3.—*Distribution of PA/NP-Employed Graduates by State*

State	*Number (Percent)*
Washington	84 (70.0)
Western	48 (40.0)
Eastern	36 (30.0)
Alaska	6 (5.0)
Oregon	6 (5.0)
Idaho	5 (4.2)
California	2 (1.7)
Other	17 (14.1)
TOTAL	120 (100.0)

PA = physician assistant; NP = nurse practitioner.

TABLE 4.—*Distribution of PA/NP-Employed Graduates by Community Population*

	MEDEX Northwest Graduates	
Community Population	*Number (Percent)*	*Cumulative Percent*
10,000	52 (40.6)	40.6
10,000-49,999	27 (21.1)	61.7
50,000-249,999 (or suburb)	19 (14.8)	76.5
250,000 (or suburb)	30 (23.5)	100.0
TOTAL	128 (100.0)	

PA = physician assistant; NP = nurse practitioner.

TABLE 5.—*Employers by Tax Status*

Category	*Number*	*Adjusted Percent*
Private for-profit	55	44.4
Public	36	29.0
Private nonprofit	33	26.6
TOTAL	124	100.0

Table 6 describes the practice setting where the respondents spend most of their time. Of note is the substantial percentage who work in solo offices (27.3 percent), health maintenance organizations (15.6 percent) and community clinics (13.3 percent). Of 125 respondents, 68 (54.4 percent) reported having formal hospital privileges.

Of our respondents, 20 percent reported working in remote satellite clinics, compared with 15 percent nationally.[5(p841)] Another 25.8 percent reported working at a rural clinic certified under the Rural Health Clinic Services Act of 1977 (PL 95-210). These are further indicators of deployment to underserved areas.

Specialty of Supervising Physician

Table 7 lists the distribution of the major specialties of physicians who supervise the respondents. This shows that 75.0 percent work with family practitioners and 83.9 percent work with primary care physicians (family or general practice, general internal medicine and general pediatrics). Nationally, about 74 percent of PA's work with primary care physicians, but only 52 percent are with family or general practitioners.[5(p841)]

A key item was noted when graduates responded to the question "Were they ultimately employed after graduation by their precepting physicians?" The answer was *yes* by 107 of 138 respondents (77.5 percent), while 22.5 percent said *no*. Common reasons for not

TABLE 6.—*Distribution by Practice Setting*

Category	*Number*	*Percent*
Solo office	35	27.3
Health maintenance organization	20	15.6
Community clinic	17	13.3
Single-specialty group	14	10.9
Multispecialty group	10	7.8
Nonprofit hospital	4	3.1
Industrial clinic	4	3.1
Government prison clinic	4	3.1
VA hospital	3	2.3
State hospital	3	2.3
City or county hospital	3	2.3
"Other" clinic	2	1.6
US Public Health Services	2	1.6
Proprietary hospital	2	1.6
PA training program	2	1.6
"Other"	2	1.6
Military hospital	1	.8
TOTAL	128	99.9

TABLE 7.—*Major Specialty of Supervising Physician*

Category	*Number*	*Percent*
Family or general practice	84	75.0
General internal medicine	8	7.1
Emergency medicine	4	3.6
Psychiatry	3	2.7
General pediatrics	2	1.8
Preventive medicine and public health	2	1.8
General surgery	2	1.8
"Other"	7	6.2
TOTAL	112	100.0

continuing in the practice included dissatisfaction by the student or preceptor (or both), and lack of patient volume to justify utilization of a PA.

Employment Characteristics

Table 8 lists selected employment characteristics for the respondents.

Of note is the job stability, with respondents averaging almost four years at their first or current job. The average workweek is similar to the national PA average of 45.6 hours.[5(p841)] The 1980 mean income ($22,486) is somewhat higher than the 1978 national figure of $17,611, even after adjusting for two years of inflation.

Board Certification Examination Results

Of 175 graduates known from file data to have taken the national PA certification examination, which was instituted in 1973, there were 163 (93.1 percent) who passed. MEDEX Northwest graduates' mean scores regularly rank in the top half of all PA program results.

Comment

These results suggest that the program is approaching its basic goal of supplying primary care practitioners to medically needy areas. Comparison with results for other PA- and physician-training programs is limited because of lack of standardized data. The nonresponse rate of 29 percent to the questionnaire survey also prevents reaching extensive conclusions. Some analysis can be made, however.

Concerning student selection, it is interesting that RN's are now an important source of PA students for MEDEX. This trend has increased recently as the supply of excorpsmen has diminished and RN's, especially those without bachelor's degrees, have increasingly sought accessible training as NP's or PA's. Organized nursing, while still willing to accept the MEDEX curriculum for PA's as adequate preparation for a registered nurse to take the national nurse practitioner certifying examination, is nevertheless concerned that some of its members are choosing the PA instead of nurse practitioner route to primary care practice.

The only significant difference noted in attrition rate was that students with more than two years of college had a lower rate than those with less. The MEDEX curriculum is condensed and very intensive, both in the classroom and preceptorship phases. It is likely that the didactic skills acquired during college help to carry a student through the heavy load of reading, note taking, and test taking.

About 60 percent of active practice MEDEX Northwest graduates work in communities of 50,000 population or less in comparison with about 48 percent of all PA's. Comparisons with other categories of health professionals are complicated by variable definitions of *rural*. Scheffler and co-workers reported that about a fourth of the US population resides in nonurban areas, where 13 percent of all physicians, 17 percent of all NP's and 33 percent of all PA's are practicing. They also found that during 1976, there were 55 percent of family physicians located in towns and cities with populations of 30,000 or less.[6] More recent data showed 69.8 percent of family practice residency graduates practiced in communities of 50,000 or less population.[7] It should be noted that these particular family practice programs emphasized rural networks of training sites.

TABLE 8.—*Selected Employment Characteristics*

Category	
Duration in first job as PA/NP	43.9 months (SD=36.9)
Duration in present job as PA/NP .	45.1 months (SD=38.6)
Number of total different jobs as PA/NP	1.7 (SD=1.0)
Hours worked per week (excluding on-call)	43.2 hours (SD=11.6)
Starting salary	$12,968 (SD=$3,428)
Current income	$22,486 (SD=$6,308)

PA=physician assistant; NP=nurse practitioner.

Perry[8] found MEDEX graduates much more likely than physician assistant or physician associate graduates to practice in rural areas. His data showed 73.3 percent of MEDEX, 48.1 percent of physician assistant and 45.6 percent of physician associate graduates in communities of under 50,000 population. A report by the Congressional Budget Office[9] showed that 37 percent of MEDEX, 18 percent of PA's, 15 percent of NP's, 8 percent of physicians and 17 percent of the general population were located in nonstandard metropolitan statistical areas of less than 50,000 population in 1976.

Why do the MEDEX graduates have a strong rural tendency? Like other health professional training programs, geographic location of education plays an important role in selection of work sites. This is reflected not only in the rural deployment that results from preceptorship, but also in the strong tendency to stay in Washington state.

One might ask whether the rural nature of Washington state is a factor since 70 percent of the practicing respondents are located there. However, data from the 1980 US census show that Washington's population is 26.4 percent rural compared with the US mean of 26.3 percent. The other northwest states served, Oregon, Montana, Idaho and Alaska, have results further above this norm (32.1 percent, 47.1 percent, 46.0 percent and 35.5 percent, respectively), but only 14 percent of the respondents are located in these states.

The Washington state PA law has also helped to promote effective PA deployment. Passed originally in 1971, it allows for practice remote from the supervising physician, prescribing of drugs, hospital privileges and temporary supervised practice as a student. This contrasts with Montana, where as of 1980 PA's were neither recognized nor certified. Given this fact, it is understandable that no graduates responded from Montana.

Besides the rural tendency, the respondents are also located in health maintenance organizations (20 percent), community clinics (13 percent) and public hospitals (7 percent). When considered with the fact that 55.6 percent are working in public or private nonprofit settings, these data suggest that graduates are an im-

portant resource for facilities outside the private, for-profit sector.

Concerning practice specialty, 90 percent of MEDEX Northwest graduates work with primary care physicians while only 58 percent of all PA's do. For family practice, the figures are 75 percent versus 42 percent. The likely reason for this is the rural preceptorship matching and placement (deployment) system utilized in the MEDEX model. Perry[8(p1020)] also found that MEDEX graduates were much more likely to be in general or family practice primary care settings than physician assistants or physician associates. He said, "The deployment system used by the MEDEX programs seems to provide a satisfactory explanation for the favorable results which they have obtained." Stated simply, if well-matched in a medically needy area to an appropriate preceptor who is willing to consider employing the student after graduation, the desired result of rural deployment is enhanced.

The increasing tendency for new family practice graduates to locate in rural settings is perceived by some observers as a barrier to further success for the MEDEX model. On the contrary, a 1978 survey of primary care physicians in Washington state showed the younger ones to be more likely to hire a PA.[10] The MEDEX Northwest program continues to find an adequate number of rural physicians for preceptors. Furthermore, family practice physicians are still reluctant to locate in smaller rural communities of population 10,000 or less which lack hospitals. PA's are showing a strong tendency to stay in this setting, especially with enactment of PL 95-210, allowing Medicare and Medicaid reimbursement to PA's and NP's in certified rural clinics.

Concerning training methodology, more than 40 PA programs have gradually moved toward a longer (24 month), more hospital-based and specialty-based training model. For example, from a peak of nine MEDEX training programs in the mid-1970s,[4(p174)] three retain the 12-month, preceptorship-oriented model. Three have adopted the longer curriculum, one has converted to NP training and two have closed.

Why is this system changing? Some probable reasons include the following:

- Pressure from academic institutions to stress biomedical rather than competency-based learning.
- Difficulty in recruiting enough rural family practice preceptors to train and hire students, especially in the eastern United States.
- Degree requirements mandating longer training periods.
- Difficulty in maintaining and monitoring quality education in rural preceptorships.
- A tendency to mimic hospital-based medical education, with a variety of specialty rotations.

Whatever the reasons, the trend in PA training toward the medical education model will have definite effects over the long run. PA graduates may begin to exhibit the specialty and geographic maldistribution characteristics of physicians. This issue has extreme importance as Congress continues to debate federal support for PA and other health manpower training programs.

The liberal PA practice laws in Washington state and strong endorsement of the Washington State Medical Association (WSMA) were two critical enabling factors in the progress of the training program. The future of the program, however, is clouded by uncertainties over state and federal funding, an increasing supply of physicians in the region and academic pressure to increase the didactic educational component. These factors undoubtedly contributed to the decision by WSMA to withdraw its endorsement of MEDEX Northwest in September 1981.

The program now plans to lengthen its didactic curriculum to 12 months, while retaining the six-month preceptorship. Tuition has been raised from $916 (in-state) or $2,623 (out-of-state) to $5,325 for all students. The recent enactment of new legislation in Montana enabling PA practice could offer new rural training and placement opportunities in a state previously resistant to the PA concept. Additional new areas of need under consideration for expanded training are occupational medicine, geriatrics and correctional medicine. An increasing number of PA's are finding employment in these settings. The program has been frequently adapted to changing conditions during its first ten years, and should continue to evolve during the 1980s.

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Book Reviews

The Western Journal of Medicine *does not review all books sent by publishers, although information about new books received is printed elsewhere in the journal as space permits. Prices quoted are those given by the publishers.*

QUALITY CONTROL—Volume 4 in METHODS IN HEMATOLOGY—Edited by I. Cavill, PhD, MRCPath, Senior Lecturer in Haematology, Welsh National School of Medicine, Cardiff, Wales. Churchill Livingstone Inc., 1560 Broadway, New York, NY 10036, 1982. 191 pages, $35.00.

Quality Control in Hematology, edited by I. Cavill, is a compilation of papers written by laboratorians predominantly in Wales and England with one contribution from California. Although a reference for quality control in hematology, coagulation and blood banks has been needed for some time in the field of laboratory medicine, the authors' attempt to do that falls short.

This book contains nine chapters and an appendix. The first chapter and the appendix deal with basic statistics and a brief historical overview of the development of statistics in industry and how they can be applied to laboratory medicine. However, as with most statistical discussions in references for quality control in hematology, the authors fail to show any straightforward way of how these statistics can be used on a day-to-day and moment-to-moment basis within a laboratory. The book as a whole assumes a considerable base of knowledge on the part of the individual reader and, therefore, will have a limited audience consisting primarily of laboratorians directly involved in hematology. Those chapters dealing with blood counting and automation are based entirely upon Coulter systems with only brief mention that these methods and techniques would be applicable to other systems. From my own experience with other major automated systems, such as the ELT-8 and the Hemalog-8, I find these chapters to show a lack of understanding by the authors of the differences between these automated instruments. Although each chapter contains some information that is of interest, especially the protocols for how to calibrate automated instruments using fresh whole blood specimens, they are disjointed and do not deal in a practical way with how these techniques should be used on a moment-to-moment basis within a laboratory. An exception to this would be chapter 7, entitled "Intralaboratory Quality Control Using Patients' Data," by Brian Bull and R. A. Korpman.

Since the Bull algorithm, as it has come to be known, is the most commonly used quality control mechanism in hematology laboratories in the United States, this book is worth the price for the excellent discussion and very practical suggestions offered by Drs Bull and Korpman on how to use the algorithm of patients' data to control automated instrumention within the hematology laboratory.

The chapters on standardization of coagulation tests and assays gives an excellent overview of what has been accomplished in England but deals only superficially with the problems faced by the wider geographic differences in the United States. In addition, although some detail for the preparation of coagulation reagents is discussed, practical suggestions as to how to use these reagents versus commercial reagents within individual laboratories on the day-to-day level are lacking.

The ninth chapter, entitled "Interpretation and Significance of Laboratory Results," was an excellent idea; however, it falls short in that it only briefly mentions the problem of systematic variance versus biologic variance in patients and it raises more questions than it answers.

This book, although useful to a limited number of people, could have been greatly improved by including a summary chapter that combines the discussion of statistics, their practical use on a day-to-day basis and the discussions of the various authors into recommendations for the quality control in hematology laboratories on a moment-to-moment, day-to-day, week-by-week basis.

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PHLEBOGRAPHY OF THE LOWER LIMB—M. Lea Thomas, MA, MB, BChir, FRCP, FRCR. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1982. 220 pages $39.00.

Acute and chronic venous diseases remain with us as common disorders that afflict both sexes and both young and old. Surprisingly, venous problems never provoke much excitement on the part of students, trainees or physicians in practice. Also, it is a field little emphasized in medical school, except perhaps for the problem of pulmonary embolism. However, even with pulmonary emboli, attention is often diverted away from the primary cause which is nearly always deep venous thrombosis of the lower limbs.

A major advance made during the lifetime of this reviewer has been the recognition of the fallibility of the bedside diagnosis of both acute and chronic venous disease. This simple fact has led to improvements in both diagnosis and treatment. This has come about by the development and implementation of noninvasive tests. The key factor in this progress has been the reemergence of phlebography as the final, definitive test. While, as noted by the author, phlebography has been with us for many decades, it still remains underutilized by the medical community. Why should this be? There are a variety of reasons which include the following: (1) it is poorly understood, (2) some radiologists find the procedure difficult and time-consuming, (3) the films are often seen as a maze of overlapping vessels whose anatomy is poorly appreciated and (4) its relevance to the clinical state is poorly understood.

While the title of the book might imply it is destined for bookshelves of radiologists, this reviewer hopes this is incorrect. I believe the text and superb illustrations should find a place in the hands of everyone interested in the problems of acute and chronic venous disease. The message is clear for those who are willing to listen. The well-performed phlebogram will often provide the necessary answers to difficult and often perplexing clinical problems.

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BETTER HEALTH WITH FEWER PILLS—Louis Shattuck Baer, MD, Burlingame, California. The Westminster Press, 925 Chestnut Street, Philadelphia, PA 19107, 1982. 168 pages, $5.95 (paperback).

The title of this little book will not immediately endear it to physician readers. Yet the central theme is neither nihilism nor holism.

Rather, Dr Baer, Clinical Professor of Medicine Emeritus, Stanford, is making a simple plea to his fellow physicians to combine the "charm" of Socrates with the "fair words" of Aesculapius when prescribing medications.

Translated, "charm" could mean "bedside manner," a term that defies definition. "Fair words" could be those healing words we give as reassurance, as well as a willingness to listen

to the words that tumble from a troubled mind or an aching heart.

Dr Baer spells out his philosophy with warm honesty, punctuated with anecdotes from his many years of practice. The doctor makes his point.

Any patient who reads this book will realize he may not need "a pill for every ill." For the physician and for the patient this slim 131-page paperback is packed with words of wisdom.

E. R. W. FOX, MD
Coeur d'Alene, Idaho
Special Editor for Idaho

* * *

DIAGNOSTIC BRONCHOSCOPY—Fourth Edition—Peter Stradling, MD (Lond), FRCP, FRPS. Churchill Livingstone Inc., 1560 Broadway, New York, NY 10036, 1981. 159 pages, 190 illustrations in color, $59.00.

The 1982 edition of this manual on bronchoscopic technique and observation maintains the high quality of the preceding editions. The text nicely describes the techniques and precautions that are generally recommended for the procedure of bronchoscopy, thus rendering it a useful guide for neophytes to this field.

Of particular note, however, is the large series of superb color plates, each accompanied by a clear explanatory drawing, that illustrate the full spectrum of endobronchial disease. This material provides an ideal reference for both experienced and novice bronchoscopists. The book's quality is excellent and everyone involved with pulmonary disease should have ready access to a copy.

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* * *

INTRODUCTION TO CLINICAL RADIOLOGY—Wallace T. Miller, MD, Professor and Vice Chairman, Department of Radiology, University of Pennsylvania School of Medicine, Philadelphia. Macmillan Publishing Co., Inc., 866 Third Ave., New York, NY 10022, 1982. 291 pages, $24.50.

This single-authored textbook presents a practical approach for an introductory radiology course in medical school. It has chapters that cover the various organ systems of the body as well as brief discussions of modern imaging techniques, including new modalities such as nuclear resonance and positron emission tomography. Initially I approached this review with some reluctance because I anticipated that an elementary textbook would not be very stimulating reading. I was mistaken in this regard, and I soon found myself engrossed in the author's clear, direct style. He punctuates the chapters with multiple examples of normal and abnormal radiographs. These are presented in a quiz fashion, and the student is expected to participate in the interpretation of the radiographic findings. This problem-solving approach keeps one's interest at all times. My only criticism of this format is that the answers are placed at the end of the textbook, and the reader must continually flip back and forth between the questions in the chapter and the answers. I found it convenient to place a paper clip on page 233 so that I could rapidly find the answer and discussion of the entity in question.

There is a section at the end of the book entitled "Differential Diagnosis" which is a valuable compilation of abnormal radiographic findings with lists of their common and uncommon causes. There are a few minor points on which I would disagree with the author: the drawings illustrating collapse of the left upper and the left lower lobe on page 45, the omission of ultrasound in the discussion of pericardial effusion and the inclusion of only one reference (at the end of the chapter on the abdominal plain films). Additional references at the end of the other sections would be helpful for the student. Lastly, the author states that 10 rads of radiation exposure for the fetus may be a cause for elective abortion. Statements from radiology, gynecology and pediatric groups in 1978 have denied this assertion, stating that no diagnostic radiation is a sufficient threat to electively warrant a therapeutic abortion.

Any radiology department that has a teaching program for medical students would find this textbook to be helpful. Physicians in training or in practice who wish to review their basic skill in interpreting radiographs, or in keeping abreast of new imaging developments, would find this book an enjoyable experience. Its relatively low price with generally high quality images make it an attractive choice.

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* * *

ORTHOPEDIC REHABILITATION—Edited by Vernon L. Nickel, MD, Professor of Surgery/Orthopedics and Rehabilitation, University of California, San Diego, School of Medicine. Churchill Livingstone Inc., 1560 Broadway, New York, NY 10036, 1982. 594 pages, $65.00.

This excellent text is a landmark in neuromusculoskeletal rehabilitation. Historically, orthopedics became a specialty with rehabilitation as its primary mission. Restoring function for the physically disabled was accomplished by a wide variety of conservative physical measures together with assistive orthotic and prosthetic devices. The required skills have continued to the present. Even though surgical procedures have come to occupy a dominant place in the care of crippling conditions, the philosophy of rehabilitation and its techniques have grown and improved to involve a wide segment of medical disciplines. Rehabilitation of the disabled has become a cornerstone of our medical and social ethic.

Dr. Nickel is a world leader in the field of orthopedic rehabilitation. His philosophy, technical skill, his ability to organize and his leadership are known and appreciated worldwide. In this volume, he has assembled authors of comparable stature. Each chapter is essentially an independent treatise covering a given subject. Nonetheless, there is a common theme throughout the book which quite effectively ties the entire contents together.

The only criticism one could find with the text would be its attempt to cover so broad a field. One could wish for more detail in certain sections. Fundamentals have not been left out, rather details of technique are abbreviated. In a text covering such a comprehensive subject, this is inevitable.

This book should be required reading for all professionals involved in physical rehabilitation. It places in perspective the various disciplines making up the rehabilitation team. The editor and chapter authors have made a significant contribution.

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MALIGNANT DISEASE OF THE VULVA—Stanley Way, FRCS(Eng), FRCOG; assisted by David Guthrie, MB, BS, MRCOG, and Peter Philips, BSc, PhD. Churchill Livingstone Inc., 1560 Broadway, New York, NY 10036, 1982. 83 pages, $24.75.

Stanley Way has, in typical British fashion, consolidated his experience in the management of vulval cancer. We are all indebted to the contribution made by him and it is with pleasure that I reviewed his book. As a learning text the book has several deficiencies. There is very little factual knowledge concerning etiology and no mention at all of the field theory of cancer change. The description of the surgical technique is "wordsome," with almost no diagramatic representations. There is no mention made as to modifying the extent of surgical therapy to match the volume and extent of disease, and the section on the surgical management of preinvasive cancer is completely inadequate in light of present knowledge. American oncologists plan deep pelvic node dissection based on the site of the lesion and the presence of disease in the uppermost femoral nodes. Way obviously is still adhering to the most radical surgical approach for every patient. Postoperative care is still very "British" and almost never used in North America.

In summary, the book is one author's collection of his very admirable results, but as a teaching textbook it has many deficiencies.

W. GARY SMITH, MD, FRCS(C)
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In Memoriam

California Medical Association

BALL, JOHN D., JR, Santa Ana. Died November 16, 1982, in Mexico of myocardial infarction, aged 57. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1952. Licensed in California in 1953. Dr Ball was a member of the Orange County Medical Association.

BILLING, ERVIN L., San Diego. Died September 26, 1982, in Del Cerro, aged 59. Graduate of the University of Louisville School of Medicine, 1952. Licensed in California in 1953. Dr Billing was a member of the San Diego County Medical Society.

BONER, ALBERT J., Beverly Hills. Died November 11, 1982, in Los Angeles, aged 86. Graduate of the University of Illinois College of Medicine, Chicago, 1923. Licensed in California in 1952. Dr Boner was a member of the Los Angeles County Medical Association.

CHANDLER, LOREN R., Palo Alto. Died October 17, 1982, in Palo Alto, aged 87. Graduate of the Stanford University School of Medicine, Palo Alto-San Francisco, 1923. Licensed in California in 1923. Dr Chandler was a retired member of the San Francisco Medical Society.

CHOJNACKI, RICHARD E., Los Altos Hills. Died August 31, 1982, in Mountain View, aged 44. Graduate of New Jersey College of Medicine and Dentistry, Jersey City, 1965. Licensed in California in 1969. Dr Chojnacki was a member of the Santa Clara County Medical Society.

COHEN, ROBERT, Bakersfield. Died September 24, 1982, in Bakersfield, aged 73. Graduate of the University of Louisville School of Medicine, 1933. Licensed in California in 1946. Dr Cohen was a member of the Kern County Medical Society.

DUNBAR, WILLIAM V., San Pedro. Died May 23, 1982, aged 83. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1927. Licensed in California in 1927. Dr Dunbar was a retired member of the Los Angeles County Medical Association.

GARRETT, NEIL, San Jose. Died September 28, 1982, in San Jose, aged 48. Graduate of Wayne State University College of Medicine, Detroit, 1960. Licensed in California in 1968. Dr Garrett was a member of the Santa Clara County Medical Society.

HILBISH, THEODORE F., San Diego. Died October 14, 1982, aged 71. Graduate of Indiana University School of Medicine, Bloomington-Indianapolis, 1937. Licensed in California in 1962. Dr Hilbish was a retired member of the San Diego County Medical Society.

ISAKSON, GREGORY, San Francisco. Died September 7, 1982, in San Francisco, aged 94. Graduate of the University of Tomsk Faculty of Medicine, Russia, 1913. Licensed in California in 1925. Dr Isakson was a member of the San Francisco Medical Society.

RICHARDSON, GEORGE C., Sonora. Died October 2, 1982, aged 76. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1932. Licensed in California in 1932. Dr Richardson was a retired member of the Tuolumne County Medical Society.

SULLIVAN, MERVYN J., Redwood City. Died September 30, 1982, of myocardial infarction, aged 64. Graduate of the Creighton University School of Medicine, Omaha, 1943. Licensed in California in 1946. Dr Sullivan was a member of the San Mateo County Medical Society.

Idaho Medical Association

WILTSE, MILTON H., Grangeville. Died November 7, 1982, aged 46. Graduate of the University of Texas Southwestern Medical School, Dallas, 1961. Licensed in Idaho in 1964. Dr Wiltse was a member of the North Idaho District Medical Society.

New Mexico Medical Society

CRANE, ROLAND R., Fort Sumner. Died October 15, 1982, in Fort Sumner, aged 76. Graduate of the University of Cincinnati College of Medicine, 1943. Licensed in New Mexico in 1945. Dr Crane was a retired member of the De Baca-Curry Roosevelt Medical Society.

MARGARD, GLENN R., Albuquerque. Died November 27, 1982, in Sun City, Arizona, aged 65. Graduate of Case Western Reserve University School of Medicine, Cleveland, 1948. Licensed in New Mexico in 1955. Dr Margard was a retired member of the Albuquerque & Bernalillo Medical Society.

Utah State Medical Association

HENRIE, JOYCE E., Salt Lake City. Died November 17, 1982, in Salt Lake City, aged 53. Graduate of the University of Utah College of Medicine, Salt Lake City, 1955. Licensed in Utah in 1960. Dr Henrie was a member of the Salt Lake County Medical Society.

NELSON, MILDRED N., Salt Lake City. Died November 27, 1982, in Murray, Utah, aged 84. Graduate of the University of Louisville School of Medicine, Louisville, 1925. Licensed in Utah in 1929. Dr Nelson was a member of the Salt Lake County Medical Society.

Wyoming Medical Society

TRELOAR, ORSON L., Afton, Died June 12, 1982, of heart disease, aged 79. Graduate of the University of Iowa College of Medicine, Iowa City, 1928. Licensed in Wyoming in 1929. Dr Treloar was a retired member of the Teton Mountain Counties Medical Society.

THE WESTERN JOURNAL OF MEDICINE
INFORMATION FOR AUTHORS

Submitting Manuscripts

Manuscripts for consideration should be sent to the editor, Malcolm S. M. Watts, MD, 731 Market Street, San Francisco, California 94103. The transmittal letter should designate one person as correspondent and include complete address, with ZIP code and telephone number.

In view of *The Copyright Revision Act of 1976,* transmittal letters should contain the following language: "In consideration for reviewing and editing my submission, the author(s) undersigned hereby transfers, assigns or otherwise conveys all copyright ownership to THE WESTERN JOURNAL OF MEDICINE in the event that such work is published by the journal." This statement should be signed by *all* the authors.

Authors are urged to seek clarity and succinctness in all manuscripts regardless of subject matter or format and to give close attention to syntax, grammar and spelling.

Clinical Investigation Section

Articles that authors wish to have considered for the Clinical Investigation section should be so designated in the transmittal letter. The type of articles appropriate for this section are those that describe experimental work in humans that extensively and prospectively examines scientific hypotheses relating to disease. An article describing a single case report will not normally be considered appropriate for this section.

Preparing Manuscripts

The original manuscript and *two* copies should be submitted on heavy bond paper (8½ by 11 inches, *not* erasable), typed double-spaced throughout (including legends, tables and references) on one side of the paper, with 1½-inch margins. Ordinarily, articles should not exceed 3,000 words (less than 15 text pages, typed double-spaced). Under exceptional circumstances only will articles longer than 4,000 words be published. Pages should be numbered consecutively, beginning with the title page.

Style

Abbreviations. Use of abbreviations should be minimized. If they are necessary, abbreviations should be spelled out at first mention, with the abbreviation itself immediately following in parentheses.

Weights and measures. All measurements should be given in metric units. English equivalents should be given parenthetically if the measurements were originally done in English units.

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Title Page

Titles are best when brief and concise. The title page should include the full name of the author(s), with degrees, academic or professional titles, complete addresses and any institutional or other affiliations. The complete name and address of the person who will handle reprint requests also should appear on this page.

Abstract

The abstract (approximately 150 words) should be a short summary, saying in brief what is said at length in the body of the article—rather than such and such "is discussed," "is presented" or "was investigated."

Tables and Figures

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Each table should be typed on a separate sheet of paper, be numbered consecutively in Arabic numerals, have a brief descriptive title and have its position indicated in the text.

Illustrations (Figures)

Three sets of clear, unmounted black and white glossy prints of figures should be submitted (preferably 5 by 7 inches, but no larger than 8½ by 11 inches). For line drawings, original artwork or glossy prints are acceptable. Illustrations should be numbered consecutively in Arabic numerals and their position indicated in the text. Figure number, first author's name and top of the photo should be shown on the reverse side of each illustration. Recognizable photographs of patients are to be masked and written permission for publication obtained from the patients.

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References

References should be limited to those cited in the text. They must be typed double-spaced and numbered consecutively as they appear in the manuscript. (See examples below for style.) Abbreviations of journal titles should conform to those used in *Index Medicus.*

Journal Articles

Note handling of multiple authorship. If more than three authors are listed as contributors, use "et al" to designate those names after the first three. Also note capitalization, punctuation, mention of inclusive page numbers, and month and year of publication. Separate the subtitle from the title by either a dash or a colon. Use colon *only* if it appears in the original citation.

1. Jones JS, Andersen HW, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978 Apr 26; 292:444-456

2. Graybill JR, Alford RH, Smith RG, et al: Cell-mediated immunity in cryptococcosis: A brief review. Cell Immunol 1978 Sep; 7:76-79

Books

Note handling of "edition," "editor(s)," and "volume," as well as appropriate sequence of reference information and capitalization of chapters and titles.

3. Berne EJ, Smith TL: Role playing in therapy, chap 2, Principles of Group Therapy. New York, Oxford University Press, 1966, pp 35-51 *(author of chapter same as author of book)*

4. Munsung JM: The role of drugs, chap 2, *In* Brest AN, Mayer JH (Eds): Hypertension—Vol 2, Therapy, 2nd Ed. Springfield, Ill, Charles C Thomas, 1961, pp 456-479 *(author of chapter different from authors of book)*

Pamphlets, Monographs or Books With No Given Author

5. AMA Department of Drugs: AMA Drug Evaluation, 3rd Ed. Littleton, Mass, Publishing Sciences Group, 1977 *(corporate author)*

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Any article accepted for publication should include the name of the journal (appropriately abbreviated) in which it will appear, and the phrase "in press" or "accepted for publication" in place of the date of publication.

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Acknowledgments

It is the policy of the *WJM* not to print acknowledgments, the feeling being that if a person has contributed enough to a paper to be mentioned, he or she should be included among the authors, or the contribution should be mentioned in the body of the paper or in a footnote.

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Role of *Clostridium difficile* and *Campylobacter jejuni* in Relapses of Inflammatory Bowel Disease

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Findings from recent studies on the role of Clostridium difficile *and* Campylobacter jejuni *in exacerbations of inflammatory bowel disease are in conflict. We examined stool specimens from 32 patients who had inflammatory bowel disease in relapse for the presence of* C difficile *and* C difficile *cytotoxin. In the last 19 cases stool specimens were also cultured for* C jejuni. C difficile *was identified in one patient who was receiving antimicrobial therapy. In no patient was* C difficile *cytotoxin detected. All cultures for* C jejuni *were negative. Routine screening of stool specimens for* C difficile *cytotoxin and* C jejuni *was not clinically useful in our patients during exacerbation of their inflammatory bowel disease.*

Several bacterial agents have been associated with relapses of inflammatory bowel disease. *Clostridium difficile* cytotoxin was commonly found in some series[1-4] but not in others.[5-9] In a single report, *Campylobacter jejuni* was implicated in exacerbations of inflammatory bowel disease,[10] but no confirmatory studies have been published.

We prospectively examined the stool specimens of patients with inflammatory bowel disease in relapse for *C difficile, C difficile* cytotoxin and *C jejuni*. We were interested in determining whether these agents would be present frequently enough to justify looking for them routinely in such patients.

Methods

Patient Population

We studied 32 patients who had inflammatory bowel disease in relapse treated at several Portland area hospitals between September 1980 and July 1981. Their mean age was 36 years and the duration of disease ranged from 2 months to 18 years. Diagnosis and classification of inflammatory bowel disease were based on clinical, radiologic, endoscopic and histologic criteria.[11] In all, 8 patients had ulcerative proctitis and 13 had ulcerative colitis with more extensive involvement; 11 patients had Crohn's disease, four had colitis, three ileitis and four ileocolitis. Symptoms were graded as mild, moderate or severe using the criteria of Trnka and LaMont.[1] The ulcerative proctitis-colitis group included five patients with mild, nine with moderate and seven with severe disease. Two patients had toxic megacolon and required surgical correction. The Crohn's disease group included two with mild, six with moderate and three with severe disease. Seventeen patients required admission to hospital.

Patients were carefully questioned regarding medication taken in the prior two months: 13 were taking sulfasalazine, 7 had taken additional antimicrobial agents and 9 were receiving prednisone.

Stool Testing

Stool specimens were collected in cardboard stool containers and transported on dry ice. Most specimens were processed within two hours and all were done within 24 hours. The *C difficile* cytotoxin assay was done on sterile stool filtrates as described by Chang and co-workers.[12] Positive controls were run simultaneously.

All stool specimens were cultured for *C difficile* using a selective medium incorporating cycloserine and cefoxitin.[13] Positive controls were run simultaneously. Colonies resembling *C difficile* were subcultured onto

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10 percent sheep blood agar and identified by an API (Analytab Products Inc, Plainview, NY) anaerobic biochemical strip.

After the report suggesting that *C jejuni* is associated with relapses of inflammatory bowel disease came to our attention,[10] stool specimens were also cultured for this organism, using a Campy-BAP medium (Baltimore Biological Laboratories, Cockeysville, Md), a selective culture medium for C *jejuni*.[14] Differentiation of *C jejuni* from other *Campylobacter* subspecies was made by detecting growth in brucella broth at 37°C and 42°C but not at 25°C.[14]

Results

The *C difficile* cytotoxin assay was negative in all 32 patients. *C difficile* itself was identified in the stool of one patient with severe ulcerative colitis; cytotoxin, however, was not present. This patient was receiving several antimicrobial agents at the time of the positive culture. He responded to conventional therapy for inflammatory bowel disease. Vancomycin was not given, and because he became asymptomatic we did not reculture specimens of stool.

C jejuni was not identified in any of the 19 patients tested.

Discussion

Inflammatory bowel disease is characterized by periods of relative well-being interspersed with flare-ups of activity. Severe relapses may lead to hospital admission and on occasion require a surgical procedure. If, as some reports suggest, treatable pathogens such as *C difficile* or *C jejuni* are frequent causes of disease exacerbation, examining all patients in relapse for these agents would be important. If they are infrequently found in patients with inflammatory bowel disease, however, routine screening may not be justifiable. It is therefore important to establish how often and under what circumstances relapses of inflammatory bowel disease are in fact associated with these agents.

Whereas our findings are in concert with several studies, others have reported *C difficile* cytotoxin in up to 60 percent of patients with a severe relapse of inflammatory bowel disease[1] and *C jejuni* has been found in 10 percent of inflammatory bowel disease relapses.[10] Possible explanations for these discrepant results include differences in test methods, patient population and local epidemiology.

Technical aspects of our study were comparable to those that suggested a significant role for *C difficile* cytotoxin in inflammatory bowel disease.[1-4] Unlike prior investigations, however, we also examined stool specimens for the organism itself. Our negative culture results in all but one case are further evidence against a significant role *C difficile* in relapses of inflammatory bowel disease in our patients, even though loss of viable organisms during transport could theoretically have occurred. Transport losses likewise may conceivably have resulted in false-negative cultures for *C jejuni,* though prompt inoculation of the culture medium in most cases makes false-negative results unlikely. A theoretically more important cause of false-negative cultures is that many patients were taking antibiotics, especially sulfasalazine. Unfortunately, the sensitivity pattern of *C jejuni* to this drug is not known.

Our patient population was comparable to that in other studies in terms of severity of symptoms and frequency of prior antimicrobial exposure. Of the 32 patients, 26 had moderate or severe disease and 17 were admitted to hospital. About half were receiving sulfasalazine or other antimicrobial agents (or both). Of the 19 patients who had stool specimens cultured for *C jejuni,* 15 had moderate or severe symptoms.

Epidemiologic factors seem the most likely explanation for the variable frequency with which *C difficile* has been found during exacerbation of inflammatory bowel disease. Recent reports have suggested that disease due to *C difficile* can be nosocomially transmitted,[15,16] and older studies of pseudomembranous colitis showed geographic and temporal clustering.[17] Series with high recovery rates of *C difficile* toxin may reflect such clustering.

We conclude that in our local hospitals neither *C difficile* nor *C jejuni* are significant agents in inflammatory bowel disease and routine screening for these pathogens in all patients with inflammatory bowel disease in relapse cannot be justified. In selected situations, however, investigation may be indicated. With *C difficile,* this would appear to be most compelling when antimicrobial agents have been administered within two months of the onset of disease symptoms. Examination for *C difficile* or *C jejuni* is also indicated in patients with exacerbation of inflammatory bowel disease during known local outbreaks and in those who fail to respond to routine treatment.

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Veterans' Reactions to Release of American Hostages

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Soon after the return of the hostages from Iran, the staff of the Mental Health Clinic of the Veterans Administration Outpatient Clinic, Santa Barbara, California, began noting an unusual association between veterans' feelings and the attention given the returning hostages. Of 100 veterans referred at random for diagnosis and treatment, not one had positive feelings about the reception given the returning hostages; 34 viewed the festivities and proclamations of welcome as excessive and unfair, and 12 expressed violent feelings toward the hostages, media people or members of the government. Of these 100 veterans, 52 expressed anxiety and excessive irritability, 41 were having psychic symptoms of depression and 38 reported sexual disturbances. This unusual form of stress had activated long-dormant feelings in veterans of four different wars and several generations.

The numerous celebrations following the triumphant return early in 1981 of the 52 hostages from Iran generally had a positive effect on the American people as a whole. Various elements of society spoke of a renewed feeling of patriotism accompanied by a feeling of "pulling together" not felt since World War II; others, of the reestablishment of world pride, to call to mind but a few such expressions of *esprit de corps*.

This instance of a major political event on the international scene that has touched us all in one way or another appears to have had a significant specificity to the feelings of a random group of veterans. Rather soon after the celebrated return of the hostages, the Mental Health staff of the Veterans Administration Outpatient Clinic, Santa Barbara (California), observed a new phenomenon. To be sure, some veterans were experiencing a regression of previously resolved or inactive symptoms, but others—representing both new and previously seen veterans at the clinic—were experiencing a heretofore unknown syndrome. These veterans cited negative feelings toward the hostages themselves, the federal government, the media and certain media people and the nonveteran public at large. Their expressed feelings ranged from mild rebukes to some quite violent tendencies.

During intake procedures and regular psychotherapy interviews, a number of veterans expressed their feelings spontaneously, while others needed some prodding to voice their emotions. It was decided to structure two questions into those otherwise unstructured interview and therapy sessions in which mention of the hostages was not volunteered. From February 12, 1981, on, we asked the following two questions:

- *How did you feel about the release of the hostages from Iran?*
- *How did you feel about the reception given the hostages on their return to the United States?*

Of the first 100 veterans (Table 1) asked these questions, not one had "highly positive" responses to the reception given the returning hostages; 34 viewed the festivities and proclamations of welcome home as excessive and unfair (Table 2), whereas 12 others (Table 3) gave vent to their feelings with rather violent expressions. The remaining 54 veterans (Table 2) had varied responses to this question, ranging from slightly negative to mildly positive. None of the veterans were negative in their responses to the first question regarding the release of the hostages. This did, however, reawaken old rescue fantasies in all six of the previous prisoners of war (POW's) in the sample who felt that their experiences were, in general, more traumatic and terrifying than those of the Iranian hostages.

Table 2 indicates that seven of group I (most hostile reactions) had no or few neurotic symptoms. A conclusion that may be drawn from the findings perhaps

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TABLE 1.—*Major Characteristics of 100 Nonpsychotic Veterans Interviewed at Veterans Administration Mental Health Outpatient Clinic Early in 1981*

	No. of Veterans
Prisoner-of-war camp stress	6
Own repatriation stress (military)	12
Delayed-stress syndrome	13
Active combat	22
Domestic problems, flare-up	30
Unsuitable civilian work	12
Sexual disturbances	38
Psychic symptoms of depression	41
Complaints of memory loss	14
Anxiety and excessive irritability	52
Receiving service-connected compensation*	37

*Service-Connected Compensation is a benefit paid to wartime or peacetime veterans. It is intended to compensate for wartime or peacetime disabilities caused by injury or disease incident to line of duty service terminating under other than dishonorable conditions.

TABLE 2.—*Degree of Neurosis of Veterans Who Expressed Violent Feelings (Group I), Those Who Viewed Welcome-Home Celebrations as Excessive (Group II) and Those Who Had Milder Reactions (Group III)*

	Group I (N=12)	*Group II (N=34)*	*Group III (N=54)*	
	No. (percent)	*No. (percent)*	*No. (percent)*	
No or mildly neurotic symptoms	7 (58.3)	20 (58.8)	21 (38.9)	48
Moderately neurotic	3 (25.0)	10 (29.4)	12 (22.2)	25
Severely neurotic	2 (16.7)	4 (11.8)	21 (38.9)	27
TOTAL	12 (100.0)	34 (100.0)	54 (100.0)	100

is that the level of neuroticism is not an indicator of intensity of an angry response. Three of the six POW's in the sample are included in group I, the other three in group II. It would appear that the POW experience lends itself to verbal expression of anger.

A comparison of Tables 1 and 2 shows no significant correlates between the level of neuroticism (mild, moderate or severe) and the statement response to the second question. In other words, there was no way of determining which group a particular veteran would fall into.

The bestowing of medals on the hostages was seen as particularly inappropriate by three veterans, all medal recipients, whose case studies are described at some length as follows:

Reports of Cases

CASE 1. The veteran in case 1 is a 66-year-old registered nurse still active in her profession. She is a slim, blond, very intelligent veteran of World War II who was a prisoner of war of the Japanese for 1,003 days in Mindanao and Manila, the Philippines. Although this woman had suffered from a number of organic illnesses and some excessive nervous tension since her discharge from active duty in 1947, she had not sought care for emotional problems in recent years. The release of the hostages, however, coincided with a return of many angry and aggressive feelings she had not experienced since her prisoner-of-war days. Her main conscious objection to the repatriation benefits awarded the former hostages was in the financial realm (Table 3). Whereas she had received but $1 a day extra pay for each of the 1,003 days endured as a POW, she felt this was scant compensation compared with the repatriation benefits awarded the former hostages. A resurgence of old feelings and hatreds also occurred. She once again objected to the general lack of recognition given US Army nurses for the courageous manner in which they handled themselves as POW's. This was followed by a comparison of the suffering and maltreatment endured at the hands of her Japanese captors vis à vis that of the treatment given the hostages by the Iranians.

While this veteran did have other concurrent stress factors in her life, her major symptomatology appeared to be linked to her ever-increasing negative and hateful feelings toward the hostages. During therapy she became increasingly depressed and did not make much progress until the headlines involving the returning hostages began to subside.

CASE 2. In this case, the veteran is a 50-year-old Mexican-American man who receives a nonservice-connected Veterans Administration pension and who had received six bronze stars for his heroic actions during the Korean conflict. Although he had not been gainfully employed since 1974 due to a low-back pain syndrome of questionable origin, he had never before visited our clinic for any medical needs. His chief symptom was the onset of dizziness immediately after learning that the returning hostages had received the Medal of Valor from the US State Department. He became suicidal soon thereafter, threatening to commit harakiri and being extremely vocal about the pain and enjoyment he would feel cutting into his abdomen and guts. Analysis showed that this patient harbored death wishes against the hostages and State Department personnel, which he could not tolerate, and later turned these wishes against himself in the form of mutilatory suicidal ideation. Within a very short time these symptoms dissipated when he became consciously aware of his negative feelings toward the hostages and the representative of the State Department extending the Medal of Valor to them (Table 1). He began to dream of some of his buddies who died in the Korean conflict and began to cry openly. This was not easy for him to do, as his personality was rather fixed to the macho image of the 1950s and that of Chicanos. Once his affectual life became more flexible, his depression lifted and to some extent his low-back pain syndrome resolved. Evidence for the latter was seen in the patient's return to playing golf (which he had once been very good at, but had not played since 1974). At the last visit he was talking of returning to work as a plumber, though he had not shown any specific action that would validate this intent.

CASE 3. The patient is a 31-year-old former heli-

TABLE 3.—*Profile and Reactions of 12 Veterans Who Expressed Violent Feelings Towards Hostages' Welcome Home Celebrations*

Case	*Age, Sex*	*Duty Period*	*Type of Military Assignment*	*Civilian Job*	*Hostage Fantasy*	*Attitude Toward Bestowing of Medals*
1	66 ♀	WW II	US Army nurse—POW	Registered nurse	"Did not deserve extra pay; we suffered more."	"Did not deserve Medal of Valor. Other medal OK."
2	50 ♂	Korean conflict	Infantry duty	Airplane hydraulics technician	"Blow up the whole of Iran with hostages in it."	"Does this mean my medals are unworthy?"
3	31 ♂	Vietnam war	Helicopter door gunner	Sheet metal worker	"Blow the hostages away."	Very negative.
4	83 ♂	WW I and WW II	Combat infantry duty—artistic talents used for propaganda purposes	Portrait painter	Drew picture representing death of hostages	Negative
5	81 ♂	WW I	Quartermaster corps	Retired salesman	Verbal abuse against hostages	Negative
6	73 ♀	WW II	Secretary on staff of US Army general	Retired social worker	"Celebrations were overdone."	"Should not receive any medals."
7	68 ♂	WW II	Army Air Forces navigator	Retired politician	"There's politics here, but there shouldn't be."	"Didn't do anything to deserve a medal."
8	70 ♂	WW II	Paratrooper—POW	Retired railroad brakeman	"Weren't really POW's; our suffering was greater."	Negative.
9	74 ♀	WW II	Secretarial staff, US Army	Retired secretary	"If they had been maltreated, but they weren't."	"Did not deserve a medal."
10	71 ♀	WW II	US Army nurse—POW	Retired registered nurse	"They were not true POW's; we suffered more."	"They deserve some recognition."
11	52 ♂	Korean conflict	Infantry duty	Realtor	"Shoot the guy who gave them Medal of Valor."	Very negative.
12	30 ♂	Vietnam war	Search and destroy unit US Army	Unemployed	"Chop up the media people."	Negative.

copter door gunner, who is presently employed as a metal worker. His reason for coming to the clinic was expressed as follows: "I feel a lot of hostility. I'm really angry that the hostages from Iran got so much more attention when they returned." Later in the interview, he related very violent thoughts (Table 3) and asked for help in dealing with these fantasies.

He was placed in an outreach group of Vietnam combat veterans and also given individual psychotherapy to resolve these and other issues that were practically paralyzing his functional abilities.

This particular veteran had attended a military academy from the seventh to ninth grades as a youngster, but during his adult military career always felt this was something that should be kept hidden from his buddies. Careful history taking found that he actually did better in military school than public school and he felt ashamed of this both at home as a child and later as an adult. Working through this material became for him the start of a growth experience and in a very short time he sublimated many of his aggressive feelings into productive areas of life and positive goal commitments.

Discussion

Of the 100 cases in the sample, none of the veterans expressed negative feelings about the actual release of the hostages. There appeared to be no significant correlation between the intensity of the response and service connection or service history. This held true even for the POW's whose own escape fantasies were restimulated. Only three POW's were classified in the group of 12 veterans who had intense responses. Age, education and civilian occupation were not seen as reference points for the veterans' emotional responses.

Whereas it is well known that there is often a long latency period between war stress and the appearance of later syndromes, such as the posttraumatic stress disorder, it is less evident as to what types of stresses can reactivate these patterns once they have become quiescent.

Characteristically, there is a definite linkage between psychotraumas of war and the reactivation of individual symptom complexes.[1] What appears to have been generated by the hostage release is a precipitation factor that crossed intergenerational lines and four different war eras and was not related to type of military assignment or civilian job. This phenomenon occurred in civilian life but affected veterans with a degree of psychotrauma similar to a war stress.

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Bronchoscopic Diagnosis of Pulmonary Infections

Comparison of Protected-Specimen Brush and Cytology Brush With Lung Aspirates

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In a recent study the use of a new plugged double-lumen protected-specimen brush with the flexible fiberoptic bronchoscope was advocated to isolate pathogens in lower respiratory tract infections while avoiding upper respiratory tract contamination. To compare the efficacy of this brush and a standard single-lumen cytology brush in identifying the etiologic agent in lower respiratory tract infections, we studied 18 patients with lung infections. Transthoracic lung aspiration was done in all but two patients in an attempt to identify the specific etiologic agent. In these two cases, cultures of specimens of blood or postmortem lung tissue yielded the causative organism. In 12 patients anaerobic or aerobic bacteria (or both) were identified, whereas one patient had a mixed bacterial and fungal infection. Using the cytology brush and the protected-specimen brush we identified at least one pathogen in 10 of 12 and 10 of 13 cases, whereas both brushes missed one or more causative organisms in 8 of 12 and 8 of 13 cases, respectively. Nonetiologic organisms were found in 8 of 12 cases by the cytology brush and 8 of 13 cases by the protected-specimen brush. Quantitative culture techniques improved the specificity of the brush results in infections where aerobes predominated. Our data show that bronchoscopic cultures of lower respiratory tract infections do not consistently recover the causative agent and are frequently subject to contamination by nonetiologic organisms. There was no difference between the brushes in avoiding contamination.

Identification of specific pathogens involved in lower respiratory tract infections continues to pose a problem. Sputum remains the most commonly used material for isolating microbes from the infected lung in spite of its proved poor yield of the true pathogens[1,2] and too often findings of false pathogens.[3,4] Transtracheal aspiration, which is thought to bypass the upper respiratory tract, has also been shown to yield both false-positive and false-negative results[5-8] and may sometimes be complicated by laryngeal spasm, bleeding, local infection and subcutaneous emphysema.[5] Flexible fiberoptic bronchoscopy appears to be a more direct method of sampling lower respiratory tract secretions but has been associated with contamination by noncausative organisms during its passage through the nasopharynx.[7-9] Additionally, local anesthetics used during bronchoscopy have been shown to inhibit bacterial and mycobacterial growth.[9-11]

Attempting to eliminate the problem of contamination and inhibition of bacterial growth by local anesthetics, Wimberley and co-workers[12] designed and carried out limited in vitro and in vivo tests on a new

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Informed consent was obtained from all patients or guardians participating in this study. This protocol was approved by the Human Experimentation Committees of all institutions involved.

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protected-specimen brush that is now marketed commercially (Medi-Tech BFW/1.0/70/90, Cooper Scientific Corporation, Watertown, Mass) for use with the flexible bronchoscope. The system consists of an inner brush surrounded by two telescoping polyethylene catheters sealed at the tip by a water-soluble plug. The inner catheter and brush are successively "telescoped" into a diseased airway and the plug extruded for sampling. The brush and catheters are withdrawn in reverse order and the brush used as a source for smear and culture material.

Although the protected-specimen brush appears to offer a new, accurate technique for sampling lower respiratory tract flora in lung infections, clinical testing of the brush has been limited, and to our knowledge no trials in humans have been done testing this brush against cultures of specimens taken from percutaneous needle aspiration of infected lungs. We therefore conducted a prospective study to evaluate the effectiveness of the protected brush versus an unprotected single-catheter cytology brush (Medi-Tech BT/1.73/58/140) in isolating pathogens from various lung infections. The isolated organisms obtained at bronchoscopy were then compared with the organisms recovered by transthoracic lung aspiration.

Materials and Methods

There were 18 patients, aged 17 to 86, who were studied during hospital admissions for pulmonary infections at the University Hospital, Oklahoma Children's Memorial Hospital and the Oklahoma City Veterans Administration Medical Center between July 1, 1979, and May 1, 1980. All patients had clinical and roentgenographic signs of lower respiratory tract infection and only those with severe, life-threatening disease or underlying illnesses such as alcoholism or preexisting pulmonary disease were accepted for this study. Patients with impaired clotting ability, advanced bullous disease or pleural effusions were excluded because of the risks involved with transthoracic lung aspiration. In two intubated patients who were being mechanically ventilated, blood cultures in one and postmortem lung tissue culture obtained within two hours of death in the other provided etiologic organisms. Nine patients had received antibiotics before study but were included because there had been no clinical response to therapy and the identity of the infecting agent was in doubt at the time of the study. The study design was approved by the Human Experimentation Committees at the institutions involved and informed consent was obtained in all cases before participation.

Transthoracic lung aspiration was done in a manner similar to that described by previous authors.[13,14] The area of consolidation was located by posteroanterior and lateral chest roentgenograms and physical findings. In two cases fluoroscopic guidance was used. In the other cases the infiltrates were situated directly adjacent to the pleura and were large enough to allow adequate localization from the roentgenograms and physical examination. With the patients seated, the skin was cleansed with povidone-iodine and 70 percent alcohol and anesthetized with 1 percent lidocaine. A 20-gauge spinal needle on a 20-ml syringe containing 3 ml of nonbacteriostatic saline was advanced into the lung parenchyma and the saline injected. Immediate suction was applied and the needle slowly withdrawn. If no material was recovered the procedure was repeated in the same or a slightly different location. A drop of the aspirate was smeared on a sterile glass slide and examined after Gram's method of staining. The remaining aspirate was inoculated into 1 ml of trypticase soy broth (Difco) and into 10 ml of prereduced chopped meat-glucose broth (Carr Microbiologicals). Within 30 minutes of collection, 0.01-ml aliquots of the trypticase soy broth suspension were plated on 5 percent sheep blood, chocolate and desoxycholate agar and incubated aerobically at 35°C. The chopped meat-glucose broth was held at 35°C until turbid, or at least five days, then subcultured using 5 percent sheep blood agar (aerobic), Schaedler's Brucella 5 percent sheep blood agar and kanamycin-vancomycin blood agar (anaerobic, 35°C) for subsequent qualitative determination of anaerobic organisms.

Flexible fiberoptic bronchoscopy was carried out with an Olympus BF-B2 fiberoptic bronchoscope. Premedication consisted of 0.6 mg of atropine given intramuscularly and the inhalation of nebulized 4 percent lidocaine for 15 minutes before bronchoscopy. With a patient in the supine position, 10 ml of 2 percent viscous lidocaine was injected intranasally and a sterile flexible nasopharyngeal airway[15] inserted so that the distal tip approached the vocal cords. After the bronchoscope was introduced through the nasopharyngeal airway and the cords visualized, 5 to 10 ml of 1 percent lidocaine was instilled onto the cords via the suction channel. No additional lidocaine was used until after the bronchial brush specimens were obtained except in cases of extreme bronchial irritability. The bronchopulmonary segment corresponding to the radiographically diseased area was visualized and entered with the tip of the bronchoscope.

Four brush specimens (two by protected-specimen brush and two by cytology brush) were collected in random order from each patient according to the methods described by Wimberley and colleagues[12] and the instructions accompanying the protected-specimen brush catheters. At the bedside, specimens from a protected-specimen brush and a cytology brush were smeared on sterile glass slides for subsequent Gram's staining and the brushes placed in prereduced chopped meat-glucose broth for qualitative anaerobic organism determination in the same manner described for the transthoracic lung aspirate specimens. The second brush of each type was placed directly into 1 ml of trypticase soy broth, vortexed and 0.01-ml aliquots plated onto 5 percent sheep blood, chocolate and desoxycholate agars within 30 minutes of collection. The plates were incubated for 48 hours at 35°C. The number of colonies,

after adjustment for dilution, were expressed as colony-forming units (CFU) per milliliter.

A suspension of *Serratia marcescens* was prepared to a concentration of 13 million CFU per ml. Three brushes of each type were dipped in the suspension, placed in 1 ml of sterile water, vortexed and plated on 5 percent sheep blood agar. Colony counts from the plates were used to determine the mean volume sampled by each type of brush.

Organisms isolated by transthoracic lung aspirate or by blood culture (one case) were considered to be causative. Organisms isolated by bronchial brush that were not found in the needle aspiration culture material were considered to be false-positive organisms.

Results

Culture of specimens of transthoracic lung aspirate or blood established a bacteriologic diagnosis in four of seven patients who had lobar pneumonia (Table 1). In the remaining three, bacteriologic diagnoses were not established, two owing to no growth on cultures of transthoracic lung aspirate and one because aspiration recovered only diphtheroids.

Culture of lung aspirate established a bacteriologic diagnosis in 9 of 11 cases of necrotizing pneumonia or lung abscess (Table 2). Six of these were due to anaerobic organisms, two to *Staphylococcus aureus* or group A β-hemolytic streptococci respectively and one to mixed facultative and anaerobic bacteria and *Coccidioides immitis*. Cultures of transthoracic lung aspirate from the two remaining patients, both of whom had prior antibiotic treatment, showed no growth.

In all, 36 organisms were identified in the cultures of transthoracic lung aspirate from 13 patients in whom diagnoses were established. From the 12 patients in whom the cytology brush was used (severe coughing forced termination of the procedure before cytology brush sampling in one patient) 16 isolates (44 percent) were identical to organisms obtained by transthoracic needle aspiration, while 20 additional isolates gave a 56 percent false-positive rate. From the 13 patients in whom the protected-specimen brush was used, 17 isolates (47 percent) were identical and 19 additional isolates gave a false-positive rate of 53 percent. The difference between brush results was not statistically significant.

Quantitative culture results from six patients in whom transthoracic lung aspiration showed aerobic organisms to be causative are shown in Table 3. Quantities of 10,000 CFU per ml or less were considered not significant. Three of six organisms isolated from cytology brush material were identical to those found by transthoracic lung aspirate, whereas four of eight isolates from protected-specimen brush material were identical. One of six isolates from the cytology brush and three

TABLE 1.—*Culture Results in Patients Who Had Lobar Infiltrates (N=7)*

Case	Age, Sex	Transthoracic Needle Aspirate	Cytology Brush	Protected-Specimen Brush	Clinical History
1	70 ♂	*Hemophilus parainfluenzae* (blood)	*H parainfluenzae* *Bacteroides fragilis* β-hemolytic streptococci Group A	*H parainfluenzae* *B fragilis* β-hemolytic streptococci Group A	Alcoholism, COPD and bilateral pneumonia; respiratory failure; temperature 41°C (106°F); mechanical ventilation; no antibiotics; blood culture positive: *H parainfluenzae*
2	44 ♂	*Streptococcus pneumoniae*	*S pneumoniae*	*S pneumoniae*	Alcoholism; acute RLL pneumonia; no antibiotics; blood culture positive: *S pneumoniae*
3	66 ♂	*S pneumoniae*	*S pneumoniae* *Peptostreptococcus* sp *Bacteroides corrodens* *Escherichia coli*	*E coli* *Staphylococcus epidermidis* α-hemolytic streptococci *Neisseria* sp	COPD; malaise, fever, chest pain, cough × 4 days; LLL pneumonia; no antibiotics; blood culture positive: *S pneumoniae*
4	17 ♀	*Pseudomonas aeruginosa* *Klebsiella pneumoniae* (autopsy)	no specimen	*P aeruginosa* *K pneumoniae* *Pseudomonas fluorescens* α-hemolytic streptococci	Acute febrile polyneuritis (Guillain-Barré syndrome); tracheostomy; ventilator × 2 months; chronic bilateral lobar pneumonia; broad-spectrum antibiotics; blood culture positive: *K pneumoniae*
5	86 ♂	Diphtheroids	α-hemolytic streptococci γ-hemolytic streptococci	α-hemolytic streptococci	COPD; weakness, weight loss, productive cough × 2 weeks; LLL pneumonia; no antibiotics
6	56 ♂	No growth	α-hemolytic streptococci	no growth	COPD; fever, chills, cough, chest pain, LLL consolidation, no antibiotics
7	25 ♂	No growth	α-hemolytic streptococci *Bacteroides melaninogenicus*	*S epidermidis*	Drug abuse; fever, chills, malaise; superior segment LLL consolidation; partially treated with broad-spectrum antibiotics

COPD=chronic obstructive pulmonary disease; RLL=right lower lobe; LLL=left lower lobe; sp=species.

TABLE 2.—*Culture Results in Patients Who Had Necrotizing Pneumonia or Abscess (N = 11)*

Case	Age, Sex	Transthoracic Needle Aspirate	Cytology Brush	Protected-Specimen Brush	Clinical History
8	50 ♂	α-Hemolytic streptococci Diphtheroids	α-hemolytic streptococci	α-hemolytic streptococci diphtheroids	Alcoholism; 1 month of fever, cough; RLL consolidation with superior segment abscess; partially treated with antibiotics
9	26 ♂	α-Hemolytic streptococci *Veillonella parvula* *Hemophilus influenzae*	α-hemolytic streptococci	α-hemolytic streptococci *V parvula*	Ethanol-related loss of consciousness 2 weeks before onset of LLL necrotizing pneumonia with superior segment abscess; partially treated with antibiotics
10	76 ♂	*Proteus morganii* α-Hemolytic streptococci *Peptostreptococcus* sp *Fusobacterium* sp *Bacteroides melaninogenicus* *Bacteroides vulgatus* *Staphylococcus epidermidis* β-Hemolytic streptococci group C or G *Klebsiella pneumoniae*	*P morganii* α-hemolytic streptococci *Peptostreptococcus* sp *Fusobacterium* sp *B melaninogenicus* *Bacteroides ramosus*	*P morganii* α-hemolytic streptococci *Peptostreptococcus* sp *Fusobacterium* sp	COPD; 2 weeks of cough, fever, chest pain; LLL necrotizing pneumonia; partially treated with antibiotics
11	60 ♂	α-Hemolytic streptococci *Clostridium histolyticum* *Propionibacterium* sp *B melaninogenicus* *Bacteroides fragilis*	*Propionibacterium* sp *B melaninogenicus* *B fragilis* *Peptostreptococcus* sp diphtheroids *Streptococcus pneumoniae* *H influenzae*	α-hemolytic streptococci *Peptostreptococcus* sp diphtheroids *S pneumoniae* *H influenzae*	Alcoholism; COPD; productive cough, chest pain, weight loss × 5 weeks; superior segment LLL abscess; no antibiotics; *Peptostreptococcus* sp grown from blood following bronchoscopy
12	55 ♂	*Propionibacterium*	*S epidermidis*	*S epidermidis*	COPD; 5 weeks productive cough, fever, weight loss; RUL necrotizing pneumonia; partially treated with antibiotics
13	25 ♂	β-Hemolytic streptococci group A	β-hemolytic streptococci group A γ-hemolytic streptococci α-hemolytic streptococci	β-hemolytic streptococci group A γ-hemolytic streptococci	3 days of fever, chills, productive cough, DOE, sore throat; LLL pneumonia with large abscess; no antibiotics; blood culture positive: β-hemolytic streptococci group A
14	63 ♂	γ-Hemolytic streptococci Diphtheroids *Fusobacterium necrophorus* *Fusobacterium nucleatum*	α-hemolytic streptococci *Neisseria* sp *Lactobacillus* *H influenzae* *S pneumoniae*	α-hemolytic streptococci *Neisseria* sp *Lactobacillus*	COPD; post herniorrhaphy; necrotizing pneumonia of LLL with superior segment abscess; no antibiotics
15	53 ♂	α-Hemolytic streptococci *S epidermidis* β-Hemolytic streptococci groups C and G *Coccidioides immitis*	α-hemolytic streptococci	α-hemolytic streptococci *S epidermidis*	COPD; chronic LLL abscess and bronchopleural fistula; productive cough; afebrile; no antibiotics
16	51 ♂	*Corynebacterium equi* *Staphylococcus aureus*	*C equi* α-hemolytic streptococci *Peptostreptococcus sp*	*C equi* *S epidermidis* *Fusobacterium* sp	Immunosuppressed renal transplant patient; cavitary lesion LUL; cough, hemoptysis, fever; partially treated with antibiotics
17	48 ♂	No growth	γ-hemolytic streptococci	no growth	Alcoholism; cough, chest pain; superior segment RLL abscess; partially treated with antibiotics
18	27 ♂	No growth	*Lactobacillus* *S aureus* β-hemolytic streptococci group D *Peptostreptococcus* sp	*Lactobacillus* *S epidermidis* *Veillonella* sp	1 year post radical neck resection; chronic aspiration; necrotizing LLL pneumonia; partially treated with antibiotics

RLL = right lower lobe; LLL = left lower lobe; RUL = right upper lobe; DOE = dyspnea on exertion; COPD = chronic obstructive pulmonary disease; sp = species.

TABLE 3.—*Culture Results From Aerobic, Quantitative Brush Specimens: Infections in Which Aerobic Organisms Were Considered Pathogenic*

Transthoracic Needle Aspirate	*Cytology Brush (CFU/ml)*		*Protected-Specimen Brush (CFU/ml)*	
β-Hemolytic streptococci group A	β-hemolytic streptococci group A	<10,000*	β-hemolytic streptococci group A	<10,000
Hemophilus parainfluenzae (blood culture)	*H parainfluenzae*	100,000	*H parainfluenzae*	100,000
	β-hemolytic streptococci group A	100,000	β-hemolytic streptococci group A	100,000
Streptococcus pneumoniae	*S pneumoniae*	100,000,000	*S pneumoniae*	100,000
S pneumoniae	*S pneumoniae*	100,000	no growth	
Pseudomonas aeruginosa	no specimen		*P aeruginosa*	1,000,000
Klebsiella pneumoniae			*K pneumoniae*	100,000
			Pseudomonas fluorescens	100,000
			α-hemolytic streptococci	1,000,000
Corynebacterium equi	*C equi*	1,000	*C equi*	<10,000
Staphylococcus aureus	α-hemolytic streptococci	<10,000	*Staphylococcus epidermidis*	100

CFU = colony-forming units.

*Species in concentrations of <10,000 CFU/ml considered not significant.

TABLE 4.—*Summary of Culture Results by Case (Diagnosis Verified by Transthoracic Needle Aspiration)*

	Cytology Brush	*Protected-Specimen Brush*	*Cytology Brush**	*Protected-Specimen Brush**
Isolated one of causal organisms ..	10/12	10/13	3/5	3/6
Missed one or more causal organisms ..	8/12	8/13	3/5	3/6
Isolated nonpathologic organisms	8/12	8/13	1/5	2/6

*Results from quantitative cultures, nonanaerobic infections. Species in concentrations of <10,000 colony-forming units per milliliter were excluded.

of eight from the protected brush gave false-positive results.

The results obtained from the 13 patients in whom a diagnosis of bacterial pneumonia or lung abscess was verified by cultures of transthoracic lung aspirate are summarized in Table 4. At least one of the organisms collected by lung aspiration was also obtained by the cytology brush in 10 of 12 cases and by the protected brush in 10 of 13 cases. Both the cytology brush and the protected-specimen brush failed to collect one or more of the causative organisms and collected false-positive species in 8 of 12 and 8 of 13 cases, respectively. None of the differences between brushes were significant using multiple contingency tables and x^2 analysis.

Isolating organisms of questionably pathogenic significance (case 5) and the no-growth results in four cases (6, 7, 17 and 18) left the cause of the lower respiratory tract infection undetermined in five patients in whom transthoracic lung aspiration was done. Three of the five had received antibiotics before collection of the culture material. In all five cases, Gram's stain of the transthoracic lung aspirate material showed abundant polymorphonuclear leukocytes but no organisms. The cytology brush collected eight isolates in four of four cases and the protected-specimen brush collected four isolates in two of four cases where no growth appeared in lung aspirate culture material.

Results of sampling a standard suspension of *S marcescens* with three brushes of each type showed that the mean volume collected by the protected brush was 0.001 ml, whereas that collected by the cytology brush was 0.004 ml.

There were three complications among the 18 patients studied. In one patient who was bronchoscoped under fluoroscopy, a small pneumothorax developed due to perforation of the pleura by one of the bronchial brushes. Aspiration of the lung was withheld two days and no intervening antibiotics were given until the pneumothorax resolved. One patient with an anaerobic lung abscess had acute bacteremia characterized by rigors, an elevated temperature of 40.5°C (105°F), confusion and positive blood cultures immediately following bronchoscopy. In one patient vasovagal syncope developed during needle aspiration. All symptoms resolved within ten minutes.

Discussion

We evaluated the accuracy of two types of bronchoscopic brushes in reproducing bacteriologic culture results obtained from blood (N = 1), postmortem lung biopsy (N = 1) and transthoracic needle aspiration (N = 16) of lower respiratory tract infections in 18 patients. We also compared the efficacy of the two brushes.

In 13 patients in whom we identified the etiologic organism(s) (mixed anaerobic or aerobic infections), the recovery rate of identical organisms was 43 percent to 47 percent for the brushes. This is lower than the 68 percent recovery rate reported in another study[16] using the same cytology brush compared with specimens from transthoracic lung aspiration. In that study, the rate of isolation of false-positive organisms was 48 percent, which is similar to our results of 56 percent for the cytology brush and 53 percent for the protected-specimen brush.

There are several possible reasons for the low brush versus needle aspiration recovery rate in our study. Sampling error could have resulted if the brushes did not reach the same area that was aspirated with the

needle. We consider this unlikely because cases were chosen for size and ease of roentgenographic anatomic location. All but two of the infiltrates involved entire lobes and, along with the abscesses, were located adjacent to the pleura for ease and safety of aspiration. Two infiltrates that were smaller were aspirated under fluoroscopic guidance. The segmental bronchus that corresponded to the area roentgenographically most densely involved by infiltrate was sampled by brush under direct vision.

A second explanation is that lidocaine administration suppressed bacterial growth. We do not consider this likely because we were very conservative in our use of lidocaine, restricting the volume to less than 10 ml in most cases. Also, our recovery rate of contaminant organisms was comparable to that of Irwin and associates,[16] a study that did not use injected lidocaine. Lidocaine should have inhibited both contaminant and pathogen growth equally.

Third, the possibility that some of the infections were nonbacterial in origin and the fact that 9 of the 18 patients received some form of antibiotic therapy before culture might have reduced brush recovery of pathogens. Both of these situations, however, would affect transthoracic lung aspiration as well as brush culture results and thus were eliminated by considering only those cases where the needle aspiration collected bacterial pathogens.

We feel that the most likely explanation for the low brush versus aspiration recovery was the possibility that sample quantity affected the yield. The amount of lower respiratory tract secretion recovered by the protected brush and the cytology brush was probably about 0.001 ml and 0.004 ml, respectively, as determined by sampling and quantitative plating of a standard solution of *S marcescens*. The amount of pus or tissue fluid inoculated into the trypticase soy broth and chopped meat glucose from the needle aspirate was 100 to 1,000 times greater. Thus, it is possible that a smaller amount of inoculum from the brushes accounted for the lower pathogen recovery rate.

The injection of lidocaine through the bronchoscope lumen has been implicated as a possible source of brush contamination.[12] We found it difficult, however, as did previous authors,[17] to bronchoscope and impossible to cannulate segmental bronchi in these persons without instilling lidocaine. To reduce possible contamination, we used a sterile nasopharyngeal airway to introduce the bronchoscope through the nasopharynx. This minimized the suction of upper respiratory tract secretions into the biopsy channel and in most cases we were able to guide the tip of the bronchoscope into close proximity with the vocal cord without touching the mucosa. Further measures to reduce contamination by nonetiologic organisms included using the supine position for all bronchoscopies and avoiding brush contact with the trachea or major bronchi during sampling.

Another explanation for contamination could be that nonetiologic organisms were already present in the bronchi before bronchoscopy in these severely ill, inhospital patients. Several authors[4,18,19] have identified single or multiple bacterial species in the trachea and major bronchi in patients who have chronic bronchitis but not in healthy subjects. Because most of our patients were smokers and nine had clinically evident chronic obstructive pulmonary disease, colonization may have played a role. Indeed, since the completion of our study, the authors who designed the brush have published a study[20] using the protected-specimen brush in 65 patients who had pneumonia. In that study, there were ten patients in whom control cultures (blood) showed single causative organisms. The rate of false-positive recovery was 44 percent, agreeing closely with the contamination rate in our study. In their study the use of quantitative cultures to eliminate organisms found in concentrations of less than 10,000 CFU per ml successfully eliminated these bacteria from consideration as pathogens. Our limited data also showed a reduction in false-positive organism recovery when the same rule was applied. However, it also reduced the recovery rate of "etiologic organisms."

We did not analyze data from the five cases in which no specific cause was determined from cultures of transthoracic lung aspirate. Three of these patients had received antibiotics before culture, which may have accounted for the lack of organism recovery. Alternatively, the infections could have been of viral origin. It is tempting to speculate that in the face of negative lung aspiration cultures, brush cultures should also be negative. This was true for two of the protected-specimen brush cultures. Because we do not know the primary pathogen it is difficult to comment on what may be contaminant. However, a recently reported study using the protected brush in 25 normal subjects with and without experimentally induced rhinovirus infections found false-positive culture results in 84 percent of the cases.[21]

These findings show that bronchoscopic collection of microbial specimens from patients with lower respiratory tract infection is inaccurate because both types of brushes failed to isolate many of the causal organisms and grew many organisms not isolated by lung aspirate cultures. There appears to be no difference in the ability of either brush to collect the offending pathogen or avoid contamination by nonetiologic organisms. Needless to say, this problem has not yet been solved and further work—especially relating to the role of quantitative cultures—needs to be done. It is important that some form of "control culture" such as transthoracic lung aspirate or blood culture be used as a comparison because the role of colonization of the lower respiratory tract in acute and chronic infections is still unknown. We wish to emphasize that this study was designed to evaluate the bacteriologic results obtained by the various methods and not the value of these methods in affecting decisions regarding antibiotic therapy.

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Medical Practice Questions

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Sleep Therapy

QUESTION:

Is sleep therapy considered to be experimental?
What is the advised length of treatment?

OPINION:

In the opinion of the Advisory Panels on Chest Diseases, Internal Medicine, Neurology, Otolaryngology/Head and Neck Surgery and Pediatrics, the evaluation, diagnosis and treatment of sleep disorders is considered accepted medical practice when performed by persons with special clinical expertise and knowledge in this field. Criteria for evaluation and diagnosis should include the following: documentation of a historical/physical examination review to establish the likelihood of a sleep disorder, a screening sleep study and more detailed study of patients (after these first two steps) to define the type of disorder.

The length of treatment required in the management of sleep disorders varies with the diagnosis. Therapy for narcolepsy, nocturnal myclonus and some sleep apnea syndromes, for example, may require a lifetime of treatment. Other problems such as medication dependency or difficulty maintaining sleep may be treated successfully on a short-term basis. The appropriate duration of treatment varies from case to case.

Therapy for sleep disorders also varies with the problem. Treatment options may range from behavioral treatments such as weight loss to surgical interventions such as a tracheostomy, septoplasty, tonsillectomy or palatopharyngoplasty.

Sleep disorder clinics usually submit their therapeutic recommendations to the patient's referring physician for continued follow-up and management.

Theophylline-Induced Seizures: Clinical and Pathophysiologic Aspects

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The clinical features and management of theophylline-induced seizures are not well appreciated in spite of their unique aspects. These seizures tend to occur in neurologically intact patients and leave no or only minor neurologic sequelae if controlled early. They begin with focal motor seizures with or without secondary generalization and are followed by stupor or coma. They are responsive only to adjustment of theophylline dosage. Should the motor phenomenon persist, it takes the form of epilepsia partialis continua. Extensive workup for a structural brain lesion may be unrewarding. The electroencephalogram typically shows periodic lateralized epileptiform discharges, which may provide a diagnostic clue.

Seizures are a potentially fatal complication of theophylline therapy. This complication represents a distinct clinical entity with several unique features. Nevertheless, the clinical diagnosis and management of theophylline-induced seizures are not as well appreciated as in other drug toxicities. The purpose of this paper is to summarize these points based on the cases reported in the literature and our experience in an attempt to delineate this form of metabolic encephalopathy. The following cases represent typical clinical examples.

Reports of Cases

Case 1. A 75-year-old man with long-standing chronic obstructive pulmonary disease was admitted for increasing dyspnea. He had no history of seizures or other neurologic diseases. Serum theophylline concentration at the time of admission was 11 μg per ml. A regimen of intravenous instillation of theophylline at 20 mg an hour was begun. On the sixth day of admission, he accidentally received intravenously 350 mg of theophylline in a period of six hours and was noted to have right focal seizures. Serum theophylline concentration at this time was 17 μg per ml, and the serum albumin level was extremely depressed (2.2 grams per dl). A metabolic workup for seizures gave unremarkable findings. An arterial blood gas determination done while the patient was receiving 100 percent oxygen showed a partial oxygen pressure (Po_2) of 257 mm of mercury, a partial carbon dioxide pressure (Pco_2) of 38 mm of mercury, and a pH of 7.37. Intravenous administration of phenytoin was begun, with a loading dose of 1,000 mg, followed by a daily maintenance dosage of 300 mg. He remained comatose, however, with occasional right facial twitching and bilateral pinpoint pupils.

An extensive workup was undertaken showing normal findings on radionuclide and computerized tomographic brain scans. An electroencephalogram showed left hemisphere periodic lateralized epileptiform discharges (Figure 1). Theophylline therapy was discontinued briefly and restarted at a rate of 20 mg an hour. Two days later, seizures stopped and the patient gradually regained consciousness within a period of a week. Serum theophylline value at this time was 8.8 μg per ml. He died a month later of his lung disease. At autopsy no abnormalities of brain and meninges were found.

Case 2. A 92-year-old woman who was known to have chronic obstructive pulmonary disease was admitted with a right hip fracture. Her serum theophylline concentration determined on admission was 16 μg per ml. Postoperatively she required reintubation due to respiratory failure and intravenous instillation of theophylline was started at a rate of 48 to 52 mg an hour. Two days later she had three left focal-onset

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ABBREVIATIONS USED IN TEXT

cAMP = cyclic adenosine monophosphate
cGMP = cyclic guanosine monophosphate
P_{CO_2} = partial carbon dioxide pressure
P_{O_2} = partial oxygen pressure

major motor seizures and became comatose with right facial twitching. A metabolic workup elicited no abnormalities. Her lowest reported P_{O_2} was 91 mm of mercury, and her highest pH was 7.49. Intravenous administration of phenytoin was started with a loading dose of 1,000 mg followed by daily maintenance dosage of 300 mg. She remained comatose, however, with occasional right facial twitching. Serum theophylline value was 24 μg per ml and the serum albumin level was greatly depressed (2.0 grams per dl). A computerized tomography brain scan showed no abnormalities. Electroencephalography showed left hemisphere periodic lateralized epileptiform discharges (Figure 2). Within 24 hours of lowering the theophylline dosage to a rate of 20 mg an hour, the patient became more alert and had no further seizures or focal neurologic findings. Serum theophylline concentration at this time was 10.5 μg per ml. She died a month later of her lung disease. A request for autopsy was not granted.

Case 3. A 95-year-old man who was known to have chronic obstructive pulmonary disease was admitted for treatment of congestive heart failure. A regimen of oral administration of theophylline was started (a loading dose of 300 mg followed by maintenance dosage of 200 mg every six hours). Two days later left focal-onset generalized seizures developed and he became comatose. Serum theophylline concentration was 20.5 μg per ml with a severely depressed serum albumin level (2.2 grams per dl). A metabolic workup gave no abnormal findings. Blood gas determination done while he was breathing room air showed a P_{O_2} of 70 mm of mercury, a P_{CO_2} of 44 mm of mercury and a pH of 7.37. Intravenously given phenytoin therapy was instituted, with a loading dose of 1,000 mg followed by a daily maintenance dosage of 300 mg. He remained comatose, however, with bilateral pinpoint pupils. A computerized tomographic scan showed only mild atrophy. Electroencephalography showed right hemisphere periodic lateralized epileptiform discharges.

He did not receive any narcotics but, because of his pinpoint pupils, 0.4 mg of naloxone was given intravenously. Before the administration of naloxone, he was deeply comatose and did not respond to any verbal or noxious stimuli. He had no spontaneous movements or seizure activities. Two minutes after naloxone was given intravenously, he responded to verbal stimuli with muttering and his pupils were noted to become slightly larger. Noxious stimuli to the supraorbital notch produced avoidance head movements. He returned, however, to his unresponsive state after ten minutes. The theophylline therapy was discontinued and he gradually regained consciousness during the next three days. He started talking and responded appropriately to verbal commands. He showed mild weakness on his left side but had no further seizures.

He died a month later of his medical problems. At autopsy his brain was mildly atrophic and no focal structural lesions to account for the mild left-sided weakness were found. The weakness was thought most likely to represent postepileptic hemiplegia (Todd's palsy).

Discussion

The cases of theophylline-induced seizures reported in other published articles, as well as here, have surprisingly constant clinical features.[1-5] These seizures are almost always focal with or without secondary generalization. The patients subsequently become stuporous or comatose. Should the motor phenomenon persist, it takes the form of epilepsia partialis continua. This clinical condition has often been referred to as focal status epilepticus, but this metabolic encephalopathy

Figure 1.—An eight-channel electroencephalogram showing repetitive epileptiform discharges across the left hemisphere at about one per second. No epileptiform discharges are seen in the right hemisphere. (Letters represent standard designations for electrode placements.)

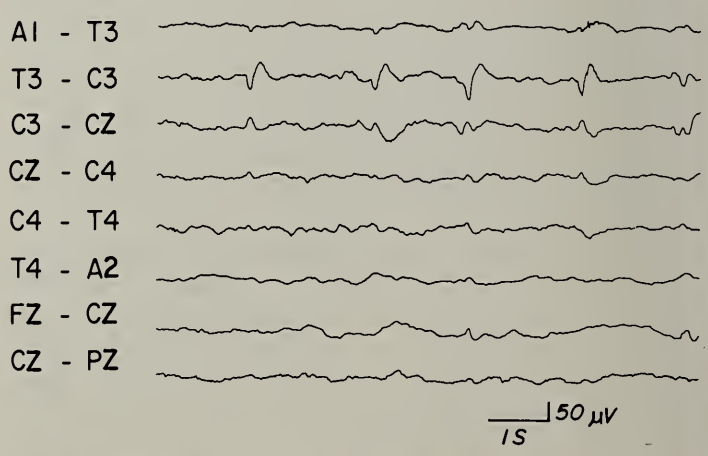

Figure 2.—An eight-channel electroencephalogram showing repetitive epileptiform discharges with phase-reversal over C-3 electrode (left central region) at one to two per second. (Letters represent standard designations for electrode placements.)

with seizures is refractory to anticonvulsant medication. There usually is no prior history of seizures or other neurologic disorders. The seizures tend to be the sole manifestation of theophylline toxicity. Their focal nature and the lack of past neurologic abnormalities tend to lead a clinician to search for a focal structural brain lesion. Prolonged encephalopathy results in a fatal outcome.

An important feature is that patients show no or only minor neurologic sequelae if the encephalopathy is controlled early. Another is that early recognition of theophylline toxicity and immediate adjustment of the theophylline dosage appear to be the only method to control this form of encephalopathy. Earlier studies emphasized high toxic serum concentrations (therapeutic range 10 to 20 μg per ml) for inducing seizures.[6,7] Because this drug is 53 percent to 65 percent protein bound, however, concomitant serum albumin levels need to be considered in the interpretation of drug concentrations.[6,8] Indeed, seizures and other signs of theophylline toxicities can occur in the face of therapeutic serum theophylline values, especially in an elderly patient with a low serum albumin level. It should also be emphasized that oral or rectal administration is sufficient to produce toxic blood concentrations.[5,6,8]

An extensive workup in search for a structural brain lesion may be unrewarding. Autopsy findings failed to show any structural brain lesions in two of our patients (cases 1 and 3). An electroencephalogram typically shows periodic lateralized epileptiform discharges or related activity, which may provide a diagnostic clue.[1-5] Periodic lateralized epileptiform discharges are an electroencephalographic entity wherein epileptiform discharges occur periodically across one hemisphere (Figures 1 and 2). This type of discharge activity is observed in two clinical categories of patients: those with acute, destructive brain lesions (for example, cerebral hemorrhage, acute infarcts and tumors), and those who have subclinical brain lesions on which are superimposed various metabolic insults (for example, alcohol withdrawal or anoxia).[9-12] Theophylline-induced encephalopathy with seizures can be classified in the second category of patients who have epileptiform discharges. Unfortunately, because the first category has received more emphasis, this valuable diagnostic clue may potentially delay the initiation of appropriate treatment. Theophylline should be considered as one of the sources of metabolic insult that can trigger periodic lateralized epileptiform discharges or related activity in the brain.

The mechanism by which theophylline produces seizures is still incompletely understood.[12,13] It has been thought to be due to its inhibitory action on phosphodiesterase, resulting in an increase in intracellular cyclic adenosine monophosphate (cAMP) levels.[1,13] In contrast, recent studies suggest that a rise in brain tissue cAMP is antiepileptic and that it is, in fact, cyclic guanosine monophosphate (cGMP) that is involved in producing neuronal epileptic discharges.[14,15] Theophylline can lead to a relative cGMP excess and hence seizure generation through its property as an adenosine receptor antagonist. It has been shown to prevent the elevation of cAMP levels induced by the convulsant drug pentylenetetrazol while not affecting cGMP levels.[14,16] Interestingly, cyclic nucleotides are thought to play a role as "second messenger" in the actions of opiates.[17] Furthermore, endorphins have been implicated in the generation of focal seizures.[18,19] In rats intraventricular administration of morphine or enkephalin produced seizures, which could be blocked by pretreatment with systemic naloxone.[18] Opiates inhibit prostaglandin E_1-stimulated cAMP formation in brain homogenates and neuroblastoma cells, whereas enkephalin and opiates increase levels of cGMP in slices of rat corpus striatum.[17] Therefore, endorphins also can lead to a relative cGMP excess and hence seizure generation.

Patients who have chronic obstructive pulmonary disease have been shown to have raised central nervous system endorphin levels.[20] Although it remains speculative, there may be a predisposing factor towards seizures in patients who have chronic obstructive pulmonary disease that is mediated by this increased endorphin activity, rendering them more susceptible to the epileptogenic effects of theophylline. The cGMP excess induced by the hyperactive endorphin state may be further enhanced by theophylline. Consonant with a heightened endorphin state are the pinpoint pupils observed in our patients (cases 1 and 3) and the transient improvement with naloxone in case 3. A common clinical metabolic insult that often triggers periodic lateralized epileptiform discharges and that is also thought to represent a hyperactive endorphin state is alcohol withdrawal. The heightened endorphin state here derives from the opiate-like catabolic derivatives of ethyl alcohol, the tetrahydroisoquinolines, which have been implicated in the degeneration of alcohol withdrawal as well.[21]

Summary

Focal-onset generalized motor seizures are a manifestation of theophylline toxicity that necessitates prompt theophylline dosage adjustment. Anticonvulsant therapy is not effective in controlling the seizures and may delay appropriate therapy, as will investigation for a structural brain lesion. These seizures tend to be the only sign of theophylline toxicity, usually occur in neurologically intact patients and leave no or only minor neurologic sequelae if controlled early. Electroencephalography done during seizure activity typically shows periodic lateralized epileptiform discharges or similar activity. Heightened endorphin activity may be the predisposing factor of theophylline-induced seizures, suggesting the possibility of treating this distinct metabolic encephalopathy with an endorphin antagonist. However, much remains to be clarified.

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Medical Practice Questions

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Percutaneous Transluminal Coronary Angioplasty (PTCA)

QUESTION:

Is percutaneous transluminal coronary angioplasty (PTCA) considered accepted medical treatment?

OPINION:

In the opinion of the Advisory Panels on Chest Diseases, Internal Medicine and Radiology, percutaneous transluminal coronary angioplasty (PTCA) is considered established medical practice for patients with medically refractory angina pectoris who have coronary artery atherosclerosis limited to a single vessel. The application of PTCA in patients with multiple vessel disease is investigational at present; review of its status is ongoing.

PTCA for single vessel disease should be done on carefully selected patients by physicians specially trained in the procedure and in facilities where the training of the PTCA team has been approved by medical staff or other peer reviewers. A cardiac surgery team should be immediately available in facilities where PTCA is done, in the event of complications.

Screening for Chlamydial Infections in Women Attending Family Planning Clinics

Evaluation of Presumptive Indicators for Therapy

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Chlamydia trachomatis was recovered from the cervices of 9.8 percent (268/2,729) of women attending seven family planning clinics. The infection rate varied from 5.5 percent to 22.5 percent in different clinics. Chlamydial infection could be associated with younger age, nulliparity, being black and use of oral contraceptives. Most (70 percent) of the chlamydial infections were inapparent and presumptive indicators for antichlamydial therapy that are useful for symptomatic women will not make a major impact on this reservoir. It is concluded that chlamydial cultures are needed to deal with the high prevalence of these infections.

Chlamydia trachomatis is a common sexually transmitted pathogen.[1] In men it causes nongonococcal urethritis and epididymitis. In women it may cause cervicitis, the urethral syndrome, endometritis and salpingitis. It is also clear that clinically inapparent infections may occur in either sex.

Because laboratory diagnosis of chlamydial infection requires tissue culture facilities that are not available everywhere, efforts have been made to identify the clinical syndromes that can be associated with chlamydial infection and to establish algorithms for the management of these conditions.[2] The goal was to develop predictors of chlamydial infection that allow for presumptive therapy in an effort to provide appropriate therapy to each woman and to reduce the large reservoir of chlamydial infections in the population.

It is estimated that approximately 3 million chlamydial infections occur in the United States each year.[3] Since there are no organized *Chlamydia* control programs it is obvious that chlamydial infections will continue to be a major problem until some efforts are made to deal with them. One such effort was the Center for Disease Control recommendation that tetracycline (2 grams per day for five days) be used to treat gonorrhea, since many men and women with gonococcal infections also have chlamydial infections. Approximately a fifth of men and a third of women with gonorrhea have double infections. Tetracycline treatment of men with gonorrhea will presumably prevent the development of *Chlamydia*-caused postgonococcal urethritis and reduce the overall prevalence of chlamydial infection. Tetracycline treatment of women with gonorrhea would also reduce the prevalence of chlamydial infections and presumably serious complications such as salpingitis.

Other presumptive indicators for antichlamydial therapy for women include having a male partner with nongonococcal urethritis, mucopurulent endocervicitis or the urethral syndrome with a laboratory workup indicating a sterile pyuria.[2]

Because men with nongonococcal urethritis (the most common clinical manifestation of chlamydial infection in men) should be treated with tetracycline or erythromycin, no additional efforts have been made to deal with the situation in men. Clearly, women are the target of any prevention program because they are at highest risk of the most serious complication of *C trachomatis* infection developing—acute salpingitis—and are epidemiologically crucial in infecting their

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sexual partners and their newborn infants, in whom serious disease may also develop.[4] The guidelines for presumptive therapy for chlamydial infection have been developed from studies of symptomatic women attending venereal disease clinics or outpatient clinics dealing with symptomatic patients. A number of other risk factors such as age, race, oral contraceptive use and socioeconomic class have also been identified.

In 1981 we conducted a survey of women attending family planning clinics in an effort to identify risk factors associated with chlamydial infection and to evaluate the efficacy of presumptive therapy in dealing with this particular patient population. The results of the study are presented here.

Materials and Methods

Population

Seven San Francisco Bay Area family planning clinics funded by the California Office of Family Planning participated in this study. Two of them were for adolescents (teen clinics—SFGH and MOF). Of the remaining five clinics, one (EO) was in an inner city poverty area, three in varying demographic areas (MAC, SJ and SM) and one in a more affluent suburb (B). The women were given pelvic examinations and cervical specimens were taken on selected days of the week to test for chlamydial infection. Data were collected on age, race, monthly income, parity, birth control method, the reason for the specific visit and clinical findings. Most women came for routine visits.

The comparisons for presumptive therapy we will make are based on previous studies carried out in this laboratory in the San Francisco Bay Area, rather than on reviews of work done in other geographic areas.[5-7]

Gonorrhea diagnosis was based on culture on Thayer-Martin medium and confirmation by oxidase test and carbohydrate degradation. In women with dysuria and frequency of urination there was a presumptive diagnosis of urinary tract infection. When urinalysis showed pyuria but no bacterial growth, the diagnosis was reported as sterile urinary tract infection (that is, the urethral syndrome[2]). Mucopurulent cervicitis was diagnosed after cleaning the cervix and finding it erythematous and edematous with a mucopurulent or purulent endocervical discharge.

Isolation of Chlamydia

The specimens were collected from within the endocervical canal by rotating calcium alginate swabs against the wall. The swabs were then placed in a tissue culture transport medium and shipped to the laboratory on wet ice and processed either the same day or the morning after they had been collected. Chlamydial cultures were carried out in cycloheximide treated McCoy cells using a modification of the procedure of Ripa and Mardh.[8]

TABLE 1.—*Screening for* Chlamydia trachomatis *in Family Planning Clinics*

Clinic (patients)	*Percent Infected*
SFGH teen (150)	18.7
MOF teen (153)	14.4
EO (111)	22.5
MAC (485)	12.5
SJ (768)	7.0
SM (974)	5.8
B (379)	5.5
TOTAL—3,020*	9.8

SFGH and MOF = teen clinics
EO = clinic in inner city poverty area
MAC, SJ and SM = clinics in varying demographic areas
B = clinic in more affluent suburb

*9.7 percent (291) specimens lost to cytopathic effects and the like; 268/2,729 valid cultures yielded *C trachomatis*.

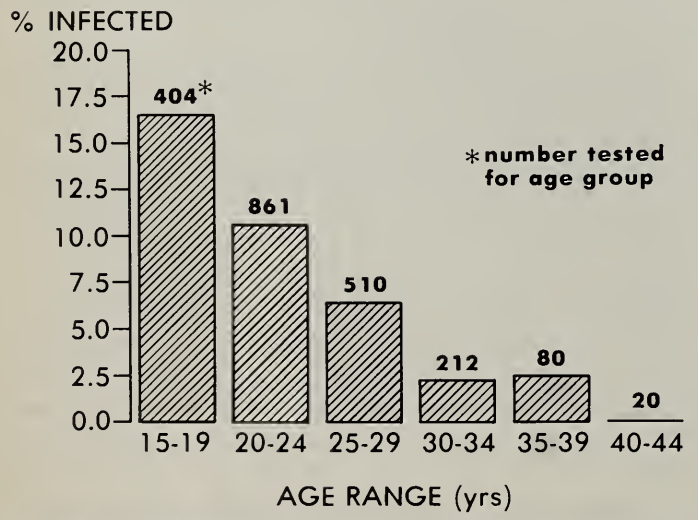

Figure 1.—Prevalence of cervical *C trachomatis* infection by age group.

Results

Table 1 presents the chlamydial recovery rates at each clinic. Approximately 10 percent of the specimens could not be evaluated because of either bacterial overgrowth or, more often, nonspecific cytopathic effects in the cell culture systems. This was particularly a problem early in the study, until we were able to assure the clinicians that the appropriate specimen for *Chlamydia* culture represented a swab of the endocervical canal and its epithelial cells rather than collection of as much material as possible. A heavy inoculum (mostly cervical or vaginal discharge) almost invariably resulted in nonspecific cytopathic effects and rendered the test invalid.

The highest recovery rate of *C trachomatis* was in the inner city clinic where 22.5 percent of the women were found to have chlamydial infections. In the teen clinics relatively high rates of infection also were found. The lowest recovery rates (5 percent to 6 percent) were in the two clinics whose clientele tended to be more middle class. The gonococcal infection rates were much lower than chlamydial infection rates at all clinics (6

percent at EO, 1.9 percent at MAC and less than 1 percent in the other clinics).

Risk Factors for Chlamydial Infection

The most easily identified risk factor for chlamydial infection is age of the population. The age distribution is shown in Figure 1. For this and further analyses, the teen clinics have been excluded. Some 16 percent of women between 15 and 19 years had chlamydial infection. The rate dropped rapidly with increasing age, to 10.8 percent of those in the 20 to 24 age group, 6 percent of those between 25 and 29 and less than 2.5 percent for those older than 30. Several other age-related variables were also associated with chlamydial infection (Table 2). *Chlamydia*-infected women were more likely to be nulliparous and never married. Oral contraceptive use was significantly associated with chlamydial infection. Black women were more likely to have a chlamydial infection than Hispanic or white women. This difference may also be related to socio-economic status in that the highest rate of chlamydial infection was seen in the EO clinic, which serves a largely black urban ghetto population. The infection rate of the relatively few whites attending that clinic was similar to that of the blacks. Similarly, the relatively few blacks in the more affluent SM population had the same general infection rate as their white cohorts. The preponderance of blacks that caused the statistically significant excess infection rate came from the MAC clinic, which has a city-wide clientele, with a likelihood that more blacks came from the poverty areas to that clinic than did whites. A higher chlamydial infection rate was found among those with lower or no income, but the reliability of economic measurements in this population is prejudiced by the clinic's income eligibility requirements. Multivariate analysis (not shown) confirmed that age was the most important risk factor for chlamydial infection. Controlling for age, the *Chlamydia*-infected women were still more likely to be black, single, nulliparous oral contraceptive users.

Presumptive Therapy for Chlamydial Infection

Most of the women attended the clinics for routine family planning care; some came for symptomatic gynecological problems; very few women came because their male partners had nongonococcal urethritis. Clinical findings were noted for 1,230 women. Some of these women were found to have gonorrhea and, of these, 45 percent had concomitant chlamydial infections (Table 3). About a third of women with signs of urinary tract infections and negative bacterial cultures and about a third of those with mucopurulent endocervicitis were found to have chlamydial infections (Table 3). For women with one of the three predictors of chlamydial infection, therefore, the overall infection rate was 35.8 percent—significantly higher than the incidence rate of 8.3 percent among women who lacked these predictors. However, if all the women with one of the three predictors had received tetracycline simply for presumed chlamydial infections, 64 percent of them would have been inappropriately treated, as the predictive value of these indicators was only 36 percent. Most of the attendees having routine pelvic examinations were asymptomatic and their pelvic examinations showed no abnormalities; therefore, the application of these indicators would have only resulted in treatment of 30 percent of the chlamydial infections in the population.

These results from the family planning clinics contrast with those previously obtained in the San Francisco Bay Area in either a venereal disease clinic or in a hospital outpatient clinic.[5-7] In those settings most chlamydial infections could be successfully treated on the basis of these predictors. In the venereal disease clinic, 60 percent of the chlamydial infections could have been dealt with by simply treating gonorrhea with tetracycline, because the 35 percent double infection rate, together with the high gonococcal recovery rate in that setting, covered the majority of the chlamydial infections (Table 4). Even higher success rates are

TABLE 2.—*Risk Factors for Chlamydial Infection of the Cervix—Routine Screening*

	Number Positive/ Number Tested (percent)	
Marital status		
Never married	171/1,575 (10.9)	$P<0.001$
Ever married	8/247 (3.2)	
Parity*		
Never pregnant	116/996 (11.6)	$P<0.001$
Ever pregnant	57/827 (6.9)	
Contraception		
Oral	149/1,146 (13.0)	$P<0.001$
None or other	40/761 (5.3)	
Race*		
Black	56/346 (16.2)	$P<0.001$
Hispanic	20/224 (8.9)	$P<0.001$
White	99/1,293 (7.7)	

*Differences not consistent for all clinics.

TABLE 3.—*Predictors of Chlamydial Infections—Routine Screening in Family Planning Clinics*

	Positive/Number (percent)	Chlamydia *Tested Positive/Number (percent)*	
Overall prevalence		132/1,230 (10.7)	$P<0.001$
Predictor positive:		39/109 (35.8)	
gonorrhea	14/31 (45.0)		$P<0.001$
endocervicitis	10/32 (31.3)		
sterile urinary tract infection	15/46 (32.6)		
Predictor negative		93/1,121 (8.3)	

TABLE 4.—*Sensitivity of Predictors of Chlamydial Infections in Different Clinics*

Clinic	*Number Predictor Correct/ Number Culture Positive (percent)*
Acute care	85/105 (81)
Venereal disease	22/36 (61)
Routine screen	39/132 (30)

projected for symptomatic women having pelvic examinations at a hospital screening and acute care clinic. In the screening clinic, where only symptomatic patients are being seen, a chart review indicated that the most common reason for *Chlamydia*-infected women to attend the clinic was lower abdominal pain. Although lower abdominal pain is not considered a presumptive indicator of chlamydial infection, most of these women had signs and symptoms of lower genital tract infection. Pelvic examination often showed an endocervicitis and therefore presumptive therapy on clinical grounds would have covered 80 percent of the chlamydial infections detected in that clinic.

In the current study, tetracycline was used for treating uncomplicated chlamydial infection (1 gram per day for 14 days) and for the treatment of gonorrhea (2 grams per day for 7 days). Posttreatment cultures were obtained from 74 women who were initially *Chlamydia*-positive and 73 (99 percent) were *Chlamydia*-negative 7 to 21 days after therapy.

Discussion

Our results confirm the high prevalence of *C trachomatis* infection in sexually active women. In these patients, most of whom were coming to clinics for routine birth control advice, chlamydial infection rates ranged from 5.5 percent to 22.5 percent in the different clinics. In only two of these clinics were gonococcal infection rates greater than 1 percent. Some of the women may have been scheduled for tests on those days when chlamydial cultures were available because the clinicians felt that certain patients might benefit from such testing. There was considerable variation from clinic to clinic in the reliability of providing the ancillary information, and there were likely differences in clinical diagnostic accuracy. The results are presented as generated with the feeling that these results probably represent more of a "real world" situation than the type of results generated in more sophisticated research establishments with highly structured protocol and extremely well trained permanent personnel.

The analyses were carried out on the basis of data submitted by the clinics. Discrepancies between the numbers used for the different analyses and the 2,729 women on whom valid chlamydial cultures had been done represent missing data on the clinic reports. For example, age was only available for 86 percent of the patients attending clinics other than the teen clinics.

Analysis of demographic characteristics showed that young and black women are more likely to be infected with *Chlamydia*. The finding that women using oral contraceptives are more likely to have chlamydial infections is also one that has been discussed elsewhere. Interpretation of this finding is difficult. *Chlamydia trachomatis* is specifically a pathogen of the squamocolumnar cells that are found within the transitional zone of the cervix. Because birth control pills can induce ectopy (a condition where the transitional zone of the cervix is moved from the endocervical canal to the ectocervix) it is possible that women taking oral contraceptives are more susceptible to chlamydial infection because more susceptible cells are exposed to infectious inocula. It is also possible that ectopy results in a more adequate sample collection and thus results in higher infection rates because of better sample collection. We did not control for patterns of sexual activity and it is possible that women using birth control pills differ from women using other forms of contraceptive in behavior patterns that would determine potential exposure to *Chlamydia trachomatis*. In other, unpublished, studies we have regularly found a significant association between oral contraceptive use and chlamydial infections. Where we have been able to control for sexual activity, we have obtained conflicting results. In some, but not all, clinics the difference in infection rates between contraceptive pill users and non-pill users disappeared when patients were matched for sexual activity. Thus, there is currently no resolution to the relationship of pill usage and chlamydial infection beyond the simple pragmatic result that women who are using oral contraceptives are more likely to have chlamydial infections.

Clearly there is a place for the application of the predictors of chlamydial infection. Our results show that they are most effective in venereal disease clinic populations and for symptomatic women. In our attempt to apply the four presumptive indicators for treatment of chlamydial infections (partner with nongonococcal urethritis, confirmed gonorrhea, sterile pyuria or mucopurulent endocervicitis) to other populations, we found these indicators only marginally useful for women attending family planning clinics for routine examinations. The sensitivity of these indicators was only 30 percent (39 chlamydial infections presumptively identified among 132 women who were culture positive). These presumptive indicators had a high specificity of 92 percent (1,028/1,121) because most of the women were *Chlamydia*-negative, asymptomatic and had normal examination findings, as one would expect in this setting. The predictive value of these indicators was 36 percent; 39 chlamydial infections were detected in 109 women with the indicators. Although these women having routine pelvic examinations had an appreciable (10 percent) overall chlamydial infection rate, we found that 70 percent of chlamydial infections were clinically inapparent. Thus, in this high-risk population one cannot avoid the need for chlamydial culture to effectively deal with this problem. A similar conclusion has been reached in a study done in a sexually transmitted disease clinic.[9]

Unfortunately, the laboratory procedures are still

quite expensive; even where they can be carried out on a relatively large scale and routinely, cost is somewhere between $20 and $30. Until a technological breakthrough introduces simpler, cheaper diagnostic tests, we are left with a situation where symptomatic women may receive appropriate therapy but the asymptomatic reservoir of chlamydial infections in women will remain. On a cost-effective basis, the simplest way of dealing with chlamydial infections would be to treat young, sexually active women with tetracyclines or erythromycin. The cost of such therapy is far less than the cost of the diagnostic testing. Since such mass therapy is obviously undesirable, the recommendation that can easily be made for that clientele is that whenever such patients are being treated for any condition for which the choice of drugs includes one effective against *Chlamydia trachomatis,* that drug should be chosen over other drugs that are not active against this organism.

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Medical Progress

Real and Perceived Risks of Medical Radiation Exposure

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There is almost no subject that elicits greater concern and less objective understanding than that of exposure of patients to radiation accompanying diagnostic radiologic procedures. One or more of the health effects (cancer, developmental abnormalties and genetic changes) attributed to low-level exposure to radiation are frequently misinterpreted as likely consequences rather than statistical risks following radiation exposure. Even less well understood is the small magnitude of the risks accompanying radiation exposure compared with those related to activities encountered during the daily routine. For this reason, the perception of risk associated with exposure to low-level radiation is inconsistent with the reality of the risk as estimated by even the most conservative models of radiation injury.

Since the beginning of time, humans have been exposed to ionizing radiation. In spite of—and conceivably in part because of—this exposure to radiation, the human species has evolved to its current state of development. Throughout life each of us is exposed to radiation from a variety of sources, some of which are an unalterable part of our environment and others are the product of our own technologic ingenuity. For example, we are all exposed to background radiation resulting from bombardment of the earth's atmosphere by cosmic rays originating in the stars and from disintegration of naturally occurring radioactive materials in the earth's crust. As a species in reasonable equilibrium with its environment, humans contain naturally radioactive materials, principally potassium 40 and carbon 14, that disintegrate and release radiation. This radiation exposes our own bodies as well as those of nearby persons. Together these sources of background radiation contribute an average of about 80 units (millirems —see below) of radiation each year to each person, with about a third of the total attributable to each of the natural sources: cosmic rays, terrestrial radiation and internal radioactive materials. Some people receive increased levels of background radiation because they live at higher elevations where the intensity of cosmic rays is greater or in geographic regions where terrestrial radiation is greater because of greater concentrations of uranium and thorium in the earth's crust. For example, the exposure of Colorado residents is about twice the background exposure averaged over the United States. Thus it has always been, and thus it shall always be.

In recent years the amount of individual exposure to radiation has been increased somewhat by the introduction of consumer products that emit radiation. For example, watches and clocks with luminous dials, television and the combustion of natural fuels for heating and cooking all contribute additional radiation (Table 1). Decisions related to life-style also affect our radiation exposure. Working in a building such as Grand Central Station or the US Capitol exposes persons to radiation emitted naturally from the granite material of the building. Living in a region of the country with above-average concentrations of radium and thorium in the soil not only increases the exposure of persons to external sources of radiation but also results in the inhalation of radon and thoron, which exposes the bronchial epithelium to highly ionizing radiation as these radioactive gases decay. When houses in these regions, especially those with basements, are made more airtight in an effort to conserve energy, they tend to trap radon and thoron and produce higher exposures of lung tissue to radiation.[1] Traveling by air adds approximately 1 unit (mrem) of radiation per hour because of the greater intensity of cosmic rays at higher altitudes. Even sleeping with another person increases

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our exposure slightly as a result of the radiation emitted by radioactive atoms contained in our bodies. As these radioactive atoms decay, they are replaced by additional radioactive atoms that enter the body through food and drink. In a cigarette smoker, as many as 8,000 units of radiation may be delivered to the bronchial epithelium of the lungs as a result of radioactivity present in tobacco leaves and released into smoke as the leaves are burned.[2]

But what is radiation? Stated simply, radiation is energy in transit from one location to another. This energy can take many forms, including visible light, sound, heat, microwaves, x-rays, β-particles and the like. Certain of these forms are energetic enough to ionize atoms and cause the disruption of molecules with subsequent biologic damage. These forms of radiation are termed ionizing radiations and are basically of three common types: α-particles, β-particles and x- and γ-rays.

TABLE 1.—*Radiation From Consumer Products*

Product	*Radiation mrem/yr*
Luminous wristwatches and clocks	1-9 to gonads
Television	0.3-1 to gonads
Coal combustion	0.2-4 to lungs
Oil combustion	0.002-0.004 to lungs
Gas ranges	6-9 to lungs
Tobacco products	up to 8,000 to lungs

mrem = millirem

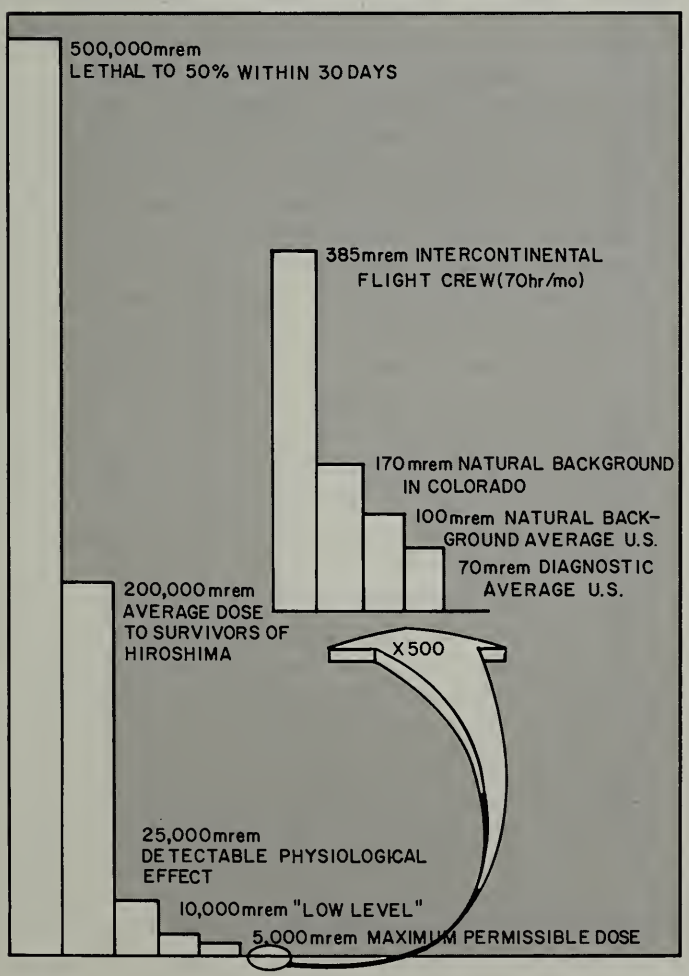

Figure 1.—Magnitude of average annual dose equivalents from various sources. mrem = millirem

An α-particle is a clump of two protons and two neutrons bound together and moving at a high velocity. α-Particles are emitted during the decay of heavy, unstable atoms such as uranium and plutonium. These are the particles that irradiate the bronchial epithelium during decay of radon and thoron inhaled into the lungs. α-Particles produce high densities of ionization along their paths but are not very penetrating. For example, an α-emitting substance on the skin is not hazardous because the particles cannot penetrate the body far enough to reach sensitive structures. On the other hand, a material that emits α-particles can be hazardous once inside the body (for example, in the lungs) because it may then encounter radiosensitive tissues.

β-Particles are also fast-moving particles emitted by radioactive atoms. They differ from α-particles in that they are much lighter and do not ionize atoms with nearly the same intensity. They are more penetrating than α-particles, however, and can penetrate a few millimeters of tissue if they are energetic enough. β-Particles actually are electrons emitted from the nuclei of radioactive atoms and may be charged either negatively (negatrons) or positively (positrons).

X- and γ-rays constitute the third type of radiation commonly encountered. These radiations are not particles; rather, they are packets (photons or quanta) of energy similar to light waves and heat but more energetic. X- and γ-rays differ only in their mode of production. γ-Rays are emitted from the nucleus as radioactive atoms decay, whereas x-rays are released during electron transitions outside the nucleus. γ-Rays are released by many radioactive atoms; x-rays are encountered most frequently in medical and dental examinations where high-voltage tubes are used to produce x-rays.

Certain units are used to describe the amount of radiation to which people are exposed. Early efforts to describe radiation quantity produced the roentgen, a unit based on the ionization created as the radiation traverses air. Although still used occasionally, the roentgen has been largely superseded by other units. A more common unit is the rad (acronym for *r*adiation *a*bsorbed *d*ose), defined as the amount of radiation causing the absorption of 0.01 joule of energy per kilogram of irradiated material. A related unit is the gray, defined as 1 J of absorbed energy per kilogram of material. That is, 1 Gy equals 100 rads, or 1 cGy equals 1 rad. The gray is becoming the preferred unit for absorbed dose.

Although the rad and the gray are extremely useful, they do not tell the whole story about radiation, because identical absorbed doses from different types of radiation produce different biologic effects. These different effects are related principally to the manner in which energy is deposited along the path of the radiation. To

express these differences, the rem (acronym for *r*oentgen *e*quivalent *m*an) has been developed as a unit of radiation quantity. The rem is a unit of dose equivalent computed as the product of the absorbed dose in rads times a modifying factor accounting for the radiation's effectiveness in causing biologic damage. The modifying factor is unity for β-particles and for x- and γ-rays, so that an absorbed dose of 1 rad yields a dose equivalent of 1 rem.

A second unit of dose equivalent is the sievert. The dose equivalent in sieverts equals the absorbed dose in grays times the modifying factor. That is, 1 Sv equals 100 rems.

With these units of radiation quantity, various sources of radiation exposure to the public can be compared. In Figure 1 it is apparent that natural sources contribute significantly to the radiation exposure of the populace and that consumer products, global fallout and nuclear power contribute far less. Also obvious in Figure 1 is the major contribution to radiation exposure of the public evolving from the medical use of radiation. Of all synthetic sources of radiation, medical uses are by far the largest contributor. As mentioned previously, the total annual amount of nonmedical radiation received on the average amounts to about 80 mrems. This exposure is matched closely by medical uses of radiation.

Within months of their discovery by Röntgen in 1895, x-rays were used medically for the detection and treatment of a variety of diseases and injuries. In just a few years, it became apparent that x-rays and other forms of ionizing radiation could have harmful as well as beneficial effects. By the mid-1920s considerable concern had arisen over the side effects of radiation exposure, including its carcinogenic properties. At this time, the process of developing protection standards for radiation exposure was begun, and that process has continued through the present. Unfortunately, a fair number of earlier experimenters with radiation, including some physicians, suffered various medical consequences following exposure to rather massive amounts of radiation in the early years of radiation medicine.

Today the amount of radiation exposure received by patients and occupational personnel involved in the diagnostic use of radiation is much lower than that received in earlier years. Consequently, the biologic effects of exposure to large amounts of radiation no longer pose a threat to the health and well-being of medically exposed persons. Instead, only long-term effects related to low levels of exposure are of concern today. For many years these effects went largely unnoticed, except for some speculation that low levels of radiation might induce occasional genetic changes in exposed persons and that these changes, while not affecting a person's health, might conceivably affect future generations. The major consequence of exposure to low-level radiation, namely an increased likelihood of cancer occurring some years following the exposure, went undetected for many years.

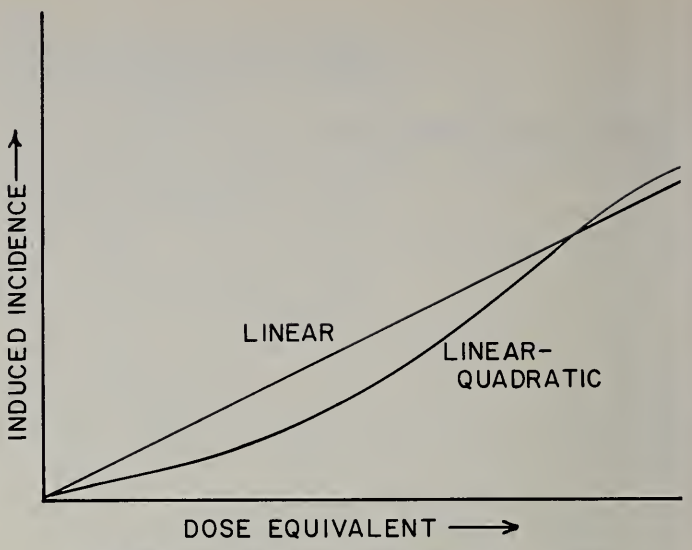

Figure 2.—Linear and linear-quadratic models.

In 1957 a report was published describing the analysis of years of data accumulated by following the survivors of Hiroshima and Nagasaki.[3] Included in the report were parallel analyses of radiologists and selected patients treated with x-rays for noncancerous conditions. This report postulated that the incidence of cancer is higher in persons exposed to radiation, and that the risk of cancer induction increases linearly with the degree of exposure. The report suggested that even a limited exposure to radiation increases the risk of cancer, albeit in a limited way. The implication of the report was that radiation-induced cancer follows a linear, nonthreshold model, and that even a low exposure to radiation increases the risk of cancer. Introduction of the linear, nonthreshold model of radiation-induced cancer generated considerable controversy that has continued to the present. Today most experts agree that the nonthreshold characteristic of the model is probably correct. These same experts believe, however, that the linear characteristic of the model probably overestimates the cancer risk from radiation exposure. In place of the linear relationship, a linear-quadratic model has been widely (but by no means universally) supported as the most appropriate predictor of cancer risk related to radiation exposure.[4] The difference between the linear and linear-quadratic models of radiation-induced cancer is shown in Figure 2.

An important feature of both curves in Figure 2 is that no threshold exists below which radiation exposure does not increase the risk of cancer in exposed persons. This feature implies that no amount of radiation exposure is absolutely safe. Although low-level exposures are accompanied by a relatively low risk, the risk is still finite no matter which model is chosen as correct.

But what is meant by "low-level exposure to radiation"? Generally, a low-level exposure is one where the dose equivalent is 10 rems (0.1 Sv) or less if received all at once, or perhaps a somewhat higher dose equivalent if received during an extended period. Essentially all medical diagnostic applications of radiation qualify as low-level exposures, as do the exposures received

TABLE 2.—*Frequency of Spontaneous Health Effects Attributable to Radiation Exposure*

Condition	*Spontaneous Frequency*
Cancer	33% lifetime incidence; 16% lifetime fatal risk
Developmental abnormalities	5% of live births
Genetic defects	10% of live births

by persons employed in the delivery of medical radiation. At these levels of exposure, three potential health risks from radiation have been identified: induction of cancer, developmental abnormalities in persons exposed in utero and inherited defects resulting from exposure of previous generations. The problem is to identify these potential risks of long-term radiation injury in as quantifiable a manner as possible.

This problem is not easily solved for a number of reasons. As shown in Table 2, cancer, developmental abnormalities and genetic defects occur spontaneously in a population. The health effects potentially induced by radiation do not differ in any detectable way from identical health effects that occur spontaneously. For example, breast cancer induced by radiation is identical to breast cancer occurring naturally without exposure to radiation. Furthermore, the additional number of cancer cases induced in a population by exposure to low-level radiation is extremely difficult to quantify in any statistically meaningful way. The only way to overcome this dilemma is to study large populations exposed to low levels of radiation. Such populations are very scarce; by far the most significant information on the health effects of radiation has been provided by studies of the survivors of Hiroshima and Nagasaki. However, these findings are from persons exposed to dose equivalents of 50 rems and more, and the extrapolation of observed effects to doses of less than 10 rads is somewhat speculative.

Induction of Cancer

By far the most well-documented effect of radiation is the induction of cancer. Much of this information is derived from the Hiroshima-Nagasaki studies. For example, a 1978 report by Beebe, Kato and Land[5] presented mortality data for 82,000 survivors followed over the period 1950 through 1974. In this population, 19,646 deaths were reported, of which 3,842 were caused by cancer. Of the latter number, 185, or 5 percent, of the deaths were attributed to radiation-induced cancer. In the range of low-level exposures, this number of radiation-related cancer deaths would be reduced by at least an order of magnitude and would be virtually undetectable with any degree of statistical reliability. This problem is illustrated in the following hypothetic example modified from an analysis by Land and co-workers.[6]

Suppose an absorbed dose of 100 rads is delivered to the bone marrow of 1,000 persons. Suppose that these persons are followed for the remainder of their lifetimes and 40 cases of leukemia are diagnosed. For the age distribution of the population at the time of irradiation, suppose that only 25 cases would be expected over the lifetimes of the 1,000 persons. Hence, an excess of 15 cases of cancer is diagnosed, and this excess (that is, 40 instead of 25 cases) is attributed to radiation.

Next suppose that the experiment is repeated, except that the population is expanded by a factor of 100 from 1,000 to 100,000, and the dose per individual is reduced by the same factor from 100 to 1 rad. According to the linear model of radiation injury, 1 rad to 100,000 persons should produce the same number (that is, 15 cases) of radiation-induced cancers as 100 rad to 1,000 persons. However, the number of cases of leukemia occurring spontaneously in the population is 100 times greater. That is, the number of cases of spontaneously occurring leukemia is now 2,500, and the radiation-induced cases increase this number to 2,515. The difference between 2,500 and 2,515 is not statistically significant, so that the presence of radiation-induced cancer in a population of 100,000 persons cannot be identified with any degree of reliability.

As a rule of thumb, a reduction by a factor of 10 in the dose to persons in a population requires an increase by a factor of 100 in the population size needed to maintain the reliability of detecting a radiation-induced injury. This rule elucidates a basic fallacy in many of the epidemiologic studies of radiation injury reported in the literature. The size of the populations studied simply is not adequate to show radiation-induced changes with any degree of statistical reliability. This conclusion is reinforced by the following statement extracted from a report on the biologic effects of ionizing radiation issued recently by the National Academy of Sciences.

None of these studies was considered by the Committee to constitute reliable evidence at present for use in risk estimation, for various reasons, including inadequate sample size in some instances, inadequate statistical analysis, and unconfirmed results.[4]

Even with this basic limitation, there is increasing evidence that the risk of cancer is increased following exposure to radiation. In particular, the incidence of breast cancer in women, thyroid cancer, lung cancer, cancer of the digestive organs and certain forms of leukemia appears to be increased following exposure to radiation at relatively high doses (>50 rems). In addition, there is some suggestion that certain tissues may be somewhat susceptible to radiation-induced cancer, whereas other tissues exhibit no increase in susceptibility whatsoever.

At low levels of exposure, the risk of radiation-induced cancer is very low. As a conservative estimate, the lifetime risk of cancer sometimes is estimated at 0.0001 for each rem of dose equivalent received uniformly over the body. Unrelated to radiation exposure, the risk of cancer developing is one third (0.33) during the lifetime of the average person. Hence 1 rem of whole-body dose equivalent increases this risk from 0.33 to 0.3301. Obviously this increase in risk is encapsulated within the statistical uncertainty of the value of one third for the incidence of spontaneous cancer.

Because of the low incidence of radiation-induced cancer and the high incidence of spontaneous cancer, large populations are required to identify any cancer increase when radiation exposures are low. One approach to this problem has been to separate the US

population into three groups related to the level of background radiation. In one group are residents of states along the Atlantic and Gulf Coastal plains where background radiation levels are among the lowest in the nation. In a second group are residents of states with intermediate levels of background radiation. These states are located in the Northeast, East, Central and Far West. In the third group are residents of states with a relatively high level of background radiation. These states constitute the Colorado plateau and include Wyoming, Colorado, New Mexico, Arizona and Utah. In these states, the radiation levels due to natural background are about twice those averaged over the United States. If the relationship between radiation exposure and cancer incidence applies to background radiation, then examination of the relative cancer rates in these three population groups could be of interest.

This examination was carried out in 1976 by Frigerio and Stowe,[7] with the results shown in Table 3. These results do not show a relationship between background radiation exposure and cancer incidence, either for all cancers in general or for the isolated case of leukemia in particular. In all likelihood any relationship that may exist is hidden by other factors such as differences in the age distribution among groups, differences in the distribution of urban versus rural populations, various levels of environmental pollution, differences in life-styles, diets, work habits and the like. That is, many other factors including those of personal choice and life-style may be more significant than radiation exposure in determining a person's susceptibility to cancer.

There is some evidence that children exposed in utero to ionizing radiation are particularly vulnerable to radiation-induced cancer. This evidence is derived mainly from retrospective studies of children exposed before birth to diagnostic x-rays, usually during a pelvimetry study.[8] These studies suggest that children exposed in utero show about a 50 percent increase in childhood cancer compared with unexposed children. The methodology of these studies is somewhat suspect and the conclusions are rather controversial; nevertheless, the studies have added to the concern over possible health effects of medical x-ray exposure during pregnancy. Consequently, most radiology facilities have implemented procedures to minimize these possible health effects.[9]

TABLE 3.—*US White Population Cancer Rates per 1 Million Persons per Year Versus Background Radiation Levels for Selected Groupings of States (adapted from Frigerio and Stowe[7])*

State Grouping	*Highest**	*Next Highest†*	*Lowest‡*
Background, mrem/yr	210	178	118
All malignant conditions ..	126.3	132.3	146.8
Leukemia	7.03	7.23	6.91

mrem = millirem

*Wyoming, Colorado, New Mexico, Arizona and Utah.
†States of the Northeast, East, Central and Far West.
‡States along the Atlantic and Gulf coasts.

Developmental Abnormalities

There is some speculation that the incidence of developmental abnormalities, as well as cancer, may be increased in children exposed before birth to ionizing radiation. This suggestion is derived from studies of animals given relatively high doses and from a few studies of the fetal effects of irradiation in women treated to high doses during radiation therapy. There is also some evidence that the incidence of microcephaly and mental retardation was increased slightly in children born in Hiroshima and Nagasaki shortly after the nuclear explosions.[10] It is not known, however, whether this finding is due to radiation exposure or to consequences such as malnutrition and fatigue. It does seem reasonable to speculate that an embryo or fetus might be particularly susceptible to radiation injury, especially during the early stages of development, because the embryo is composed of relatively few cells, which are fairly undifferentiated and undergo a high rate of division.[11]

At low levels of exposure, the risk of a radiation-induced developmental abnormality is very small. When compared with the natural risk of 4 percent to 6 percent that a child will show some developmental abnormality at birth or shortly thereafter, the risk of a radiation-induced abnormality seems even smaller. Hence, the National Council on Radiation Protection and Measurements has issued the following statement concerning radiation and pregnancy.

> For any individual case, the increased risk of such effects from doses below the 10 rad level received at any stage of pregnancy, according to the best knowledge available today, is small compared to this normal risk (4 percent to 6 percent). . . . the risk of malformation is significantly increased above control levels at doses of about 15 rads. Therefore, the exposure of the fetus to radiation arising from diagnostic procedures would rarely be cause, by itself, for termination of pregnancy.[9]

Even though the risk of inducing an abnormality in a developing fetus is very small, it may not be entirely nonexistent. Hence, the exercise of caution during abdominal exposures of pregnant and possibly pregnant women is a prudent course of action. Whenever an x-ray study is necessary in the abdominal region of such a person, modifications in the study are recommended to reduce the exposure to a fetus should one be present.

Genetic Effects

Genetic damage is the third major category of risk from radiation exposure. For many years, this risk was considered to be greater than all others; today, however, it is considered to be no greater, and possibly less, than the risk of cancer induction following exposure to radiation. All of the information concerning the genetic hazards of radiation is derived from experiments on animals and lower forms of life. No definitive evidence has ever been accumulated to show radiation-induced genetic effects in humans, despite a fair number of population groups that have been monitored following exposure to radiation in an effort to identify radiation-induced genetic damage.[12] By far the largest group

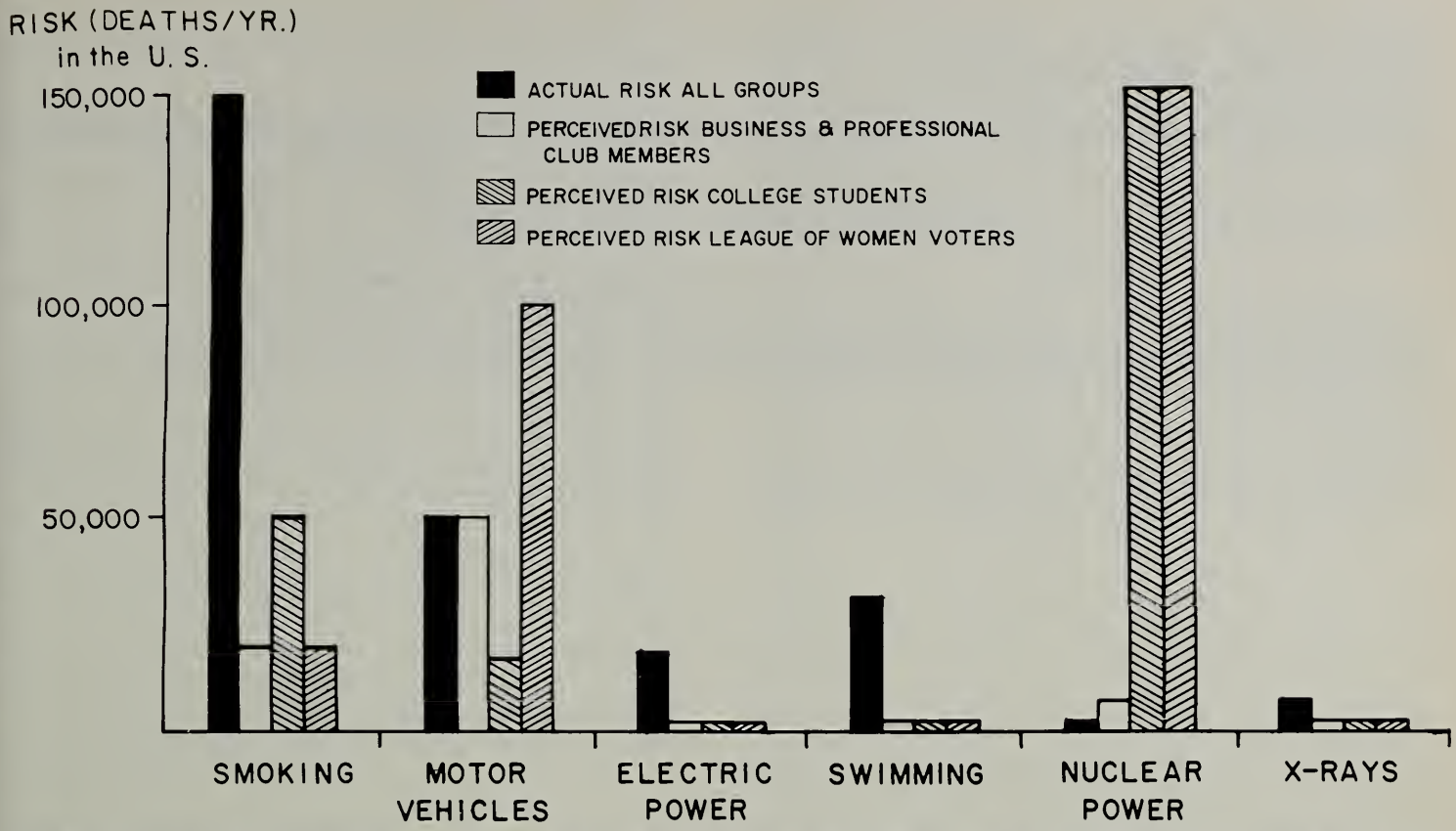

Figure 3.—Actual and perceived risks of various societal activities as determined by Decision Research, Inc. of Eugene, Oregon (adapted from Sinclair[13]).

studied has been the first- and second-generation descendants of the Hiroshima and Nagasaki survivors. No genetic effects attributable to radiation have been noted in either of these generations, in spite of the relatively large exposures received by the parents or grandparents.

A number of factors may contribute to the absence of observable genetic effects in the populations studied. Genetic abnormalities occur spontaneously in about one of every ten human births. Consequently, the number of radiation-induced abnormalities would have to be rather large to be identifiable in the setting of naturally occurring abnormalities. Like other radiation-induced effects, genetic abnormalities caused by radiation do not differ in any measurable way from those arising spontaneously. Furthermore, most mutations are recessive and may not be expressed phenotypically in a population until enough mutations are present to make the likelihood significant that carriers of recessive mutations will mate. A third possibility is that the genetic hazards of radiation exposure are quite small and have been overestimated by the public and by various advisory groups. From the existing evidence, none of the possibilities can be eliminated; hence, the use of radiation under the safest conditions reasonably achievable continues to be the most prudent course of action.

Summary

After considering all the evidence related to the health effects of exposure to low levels of radiation, it is apparent that the risk is immeasurably small to any single person in a population exposed to small amounts of radiation. However, multiplying this immeasurably small estimate of risk by very large populations yields numbers that seem to imply that significant health effects occur following exposure to small quantities of radiation. Although many advisory groups have cautioned against this procedure and conclusion, they continue to be used by well-meaning scientists and political action groups. This process distorts the risk of radiation exposure as perceived by the public. Findings depicted in Figure 3 indicate the magnitude of this distorted perspective.

In a public opinion poll conducted by Decision Research, Inc. of Eugene, Oregon, three groups were asked to rank the relative risks of various societal activities.[13] Two of the three groups ranked nuclear power as the most hazardous of all societal activities, with a risk factor greater than that for smoking, automobiles, handguns and alcohol. The third group was a bit more realistic, ranking nuclear power eighth in the list of hazardous activities. Actually, nuclear power is the least hazardous of all 30 of the activities included in the poll.

It is a conservative posture and probably a wise course of action to assume that exposure to any amount of radiation, no matter how small, carries with it some element of risk. For example, requests for x-ray studies and nuclear medicine procedures should always be accompanied by an appreciation of the possibility of risk to the patient. Any examination request should reflect an evaluation of the benefits to be derived balanced against the possibility of risk. A similar appraisal

should be applied to our own exposures to radiation in applying radiation health care. At the same time, this element of risk should be placed in a realistic perspective by comparing it with other risks we and our patients assume every day, often without thinking about them at all. It is only through such an approach that the small but possibly finite risks of low-level exposure to radiation can be placed in a realistic perspective.

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Radiation and Health

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Professor Hendee discusses some of the important problems of patient exposure to medical x-rays, and he does it well.[1] But there are certain issues Professor Hendee's article addresses but does not clarify sufficiently to provide guidance on radiation and health for a busy practitioner of medicine. What is low-level radiation and why is it of concern? What are the radiation doses we are dealing with in diagnostic radiology and should these exposure levels be reduced? Is there potential harm from diagnostic radiation exposure? And is x-ray exposure during pregnancy dangerous to the developing embryo and fetus?

What Is Low-Level Radiation?

While there is no precise definition of low-level radiation, low-level exposure or low-dose radiation, scientists generally agree that low-level radiation is that which falls within the dose range considered permissible for occupational exposure. According to the accepted standards of the International Commission on Radiological Protection (ICRP), 5 rems (0.05 sievert [Sv]) per year to the whole body would be an allowable upper limit of low-level radiation dose for the individual radiation worker.[2] In this context it could be concluded that prolonged exposure to these levels of diagnostic radiation or prolonged periods of occupational exposure among radiation workers are considered by some scientists to cause delayed radiation health effects, such as cancer or hereditary defects. Other scientists strongly dispute this and firmly believe that low-level radiation is nowhere nearly as dangerous as their colleagues would contend.[3] The issue is a difficult scientific one because such health effects, if any do occur, are so rarely seen from low-level radiation because the exposures are so small. The issue of this scientific dispute may never be resolved—it may be beyond the abilities of science and mathematics to decipher.[4]

What Are Some of the Radiation Doses From Common X-ray Procedures?

The radiation doses from x-ray examinations are limited to defined regions of the body; the radiant energy absorbed by the tissues is generally much the same wherever the procedure is done in the United States.[5] For a chest x-ray study, the dose to the bone marrow in the thorax—the important target tissue—is about 10 to 20 mrads (0.1 to 0.2 milligray)* per projection. For the hip and upper femur, the dose is about 75 mrads (0.75 mGy). And for dental radiography, a complete mouth examination may involve 10 mrads (0.1 mGy) to the bone marrow. Mammography today ranges about 1 to 5 rads (0.01 to 0.05 Gy), but new techniques permit this to be reduced to only 0.5 rad to the breast per study. A barium enema is a "high-dose" examination—the average is close to 1 rad (0.01 Gy), but it could be as high as 3 rads (0.03 Gy). Special radiologic procedures, such as angiography of the abdomen, may be as low as 400 mrads (4 mGy), but can be much higher. Computerized tomography (CT) scans of the brain may involve a dose as high as 4 rads to the portion of the brain exposed; but the new CT units have decreased this to a range of about 1 rad or 0.01 Gy. X-ray pelvimetry to the pregnant mother ranges from 600 mrads (6 mGy) to about 1 rad (0.01 Gy); the fetus receives a dose of about half this amount.

Are the Epidemiologic Studies on Radiation Carcinogenesis in Human Populations Valid?

The epidemiologic evidence is compelling—cancer arising in a variety of organs and tissues and transmitted genetic effects are the principal late effects in populations of exposure to low levels of ionizing radiation.[2,3,6-8] Since the late 1940s and early 1950s, it has been postulated that there may be no threshold level of exposure to ionizing radiation below which risks of injury are entirely lacking. At the same time, however, it has been recognized that the risks of exposure at levels of natural background can be estimated only by interpolation between levels of health effects observed at high doses and

*In the new system of international units, 1 Gy (gray) = 100 rads, and 1 Sv = 100 rems.

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dose rates and spontaneous levels of the same effect. The assumption of a linear, no-threshold dose-response relationship (linear hypothesis) has generally been considered to provide a conservative approach to risk estimation for low-dose and low-dose-rate exposure, because the effect per unit dose for low-linear energy transfer (LET) radiations (for example, x-rays and γ-rays) has usually been observed in biology and medicine to decrease with decreasing dose and dose rate.[7]

Several reports have been published, some recently, that seem to indicate degrees of carcinogenic radiation effects at low doses in humans that would be incompatible with a conservative linear hypothesis. This would lead to claims that low-level exposure, in fact, may be more hazardous per unit of absorbed dose than at high doses and dose rates. These data and claims, therefore, suggest that this dose-response relationship at low doses does not lead to conservatism, but may even underestimate the effects of low doses and low dose rates. However, each of these epidemiologic studies provides information that has been heavily criticized for serious statistical and methodologic difficulties and, individually or collectively, are not scientifically convincing enough to argue against either the conservatism of the linear hypothesis or the present estimate of risk of cancer induction in human populations exposed to low levels of ionizing radiation.[3,7] They stand apart from, and in disagreement with, the large body of epidemiologic evidence that convincingly shows the carcinogenic and hereditary effects in humans after exposure to low doses and low dose rates.

Are There Any Contraindications to Diagnostic X-ray Examinations?

There are no contraindications to any medical examination; rather, there are indications for a clinical examination. X-ray procedures, however, have an unwanted by-product that is of no benefit to the patient, namely, ionizing radiation that is absorbed by the cells and tissues of the body. A good rule, therefore, is never to expose a patient to unnecessary radiation, and to expose the patient only to that amount of radiation which provides the diagnostic radiologic information.

There are, however, special circumstances to consider because there is a benefit to be gained for a patient's health, and this is invariably associated with the risk of radiation injury resulting in an increased probability of delayed or late health effects occurring in that patient. Probability is the mathematical chance of something occurring; risk is when that probability is associated with a detriment, such as ill health. When the benefit strongly outweighs the risk, then we are not as concerned—as, for example, radiation exposures attendant in specialized procedures, such as examination of the coronary arteries in a patient with cardiovascular disease, or computerized tomography of the brain in a patient with a possible cerebral hemorrhage. In these cases, the benefit-to-risk ratio is high.

But there are occasions when the benefit to the patient of a diagnostic radiologic procedure is small or even negligible, and the attendant risk of radiation exposure, though equally small, may become relatively high; that is, the benefit-to-risk ratio is low or the risk may be even greater than the potential benefit. The best examples here are the mass screening x-ray studies, for example, chest photofluorography for tuberculosis or lung cancer in asymptomatic populations and screening mammography in women with extremely low breast cancer risk, such as women younger than 35 years of age who do not have breast cancer risk factors. That is why the American College of Radiology recommends that such mass x-ray screening programs of asymptomatic populations that result in low diagnostic yields not be undertaken.

Is There Potential Harm From Diagnostic Radiation Exposure?

There is always the potential for harm from exposure to ionizing radiation such as x-rays. Ionizing radiation has several injurious effects, such as cataracts of the lens of the eye and impaired fertility, but three late or delayed health effects stand out as those of greatest concern—carcinogenesis, or cancer induction; teratogenesis, or developmental abnormality of the newborn; and mutagenesis, or genetically related ill health occurring in descendants of exposed persons.[9] Scientists now believe that exposure to ionizing radiation—because of the structure and function of the important living molecules, the DNA molecules within the cell and the manner in which energy is deposited in the molecular structure—increases the probability of such deleterious health effects. Further, as the dose of radiation increases above low levels, the risk of these deleterious effects increases in exposed human populations. However, these events at the biophysical level of the cell are extremely rare, due primarily to the efficiency of repair of radiation injury.[7] Even when injurious radiation effects occur, resulting in a lesion in the DNA molecular structure, the cells and tissues have an enormous capacity to repair the radiation damage, so that no residual injury remains.[7] Because such health effects, if any, are so rarely seen from low-level radiation, and because the health effects induced by radiation are indistinguishable from those occurring naturally, it follows that their existence can be inferred only on the basis of a statistical excess above the natural incidence in exposed populations.[3] Thus, at the dose levels of diagnostic radiologic exposure normally encountered in radiologic procedures in the United States, it follows that there is only a very slight probability of increased deleterious health effects re-

sulting from diagnostic radiation exposure of about 100 million Americans each year.

Is X-ray Exposure During Pregnancy Especially Dangerous?

If there are indications for examination of the fetus or pelvis, where pelvimetry or obstetric abdominal examination will provide the diagnostic information, then x-ray studies can be carried out safely.[10] Circumstances exist, however, in which a series of x-ray studies are done for diagnosing ill health in the mother and, on occasion, there is no knowledge that a pregnancy exists. Each situation is then weighed according to the benefits and risks, inevitably the risks to a fetus. There are two delayed health effects of concern. The first is developmental abnormality in the newborn resulting from radiation teratogenesis during the first trimester when the fetus is unusually susceptible to radiation injury.[8] Here, teratogenesis is strongly dependent on the stage of gestation at which exposure occurs. Evidence from the Japanese atomic bomb survivors suggests decreased head size associated with mental retardation has occurred from exposure in utero to dose levels below 10 rads (0.1 Gy).[3] The second delayed health effect is cancer induction, notably leukemia, resulting from x-ray doses in the range of 1 to 2 rads (0.01 to 0.02 Gy) following exposure in utero during the last trimester.[3] One study strongly suggests this conclusion, with another ten or so tending to support the findings of this study.[11] Evidence is mounting, however, that indicates too many biases in the one positive study and, in fact, certain of the findings on childhood cancers may prove to be spurious.[12] The controversy is not settled, but the introduction of ultrasound pelvimetry as the primary method of examining the fetus and the pregnant abdomen is making the conclusion of the controversial study somewhat academic.

The "ten-day rule" is a recommendation that x-ray examination of a woman's abdomen be done only during the ten-day interval between the onset of the patient's menstrual period and the tenth day thereafter. It is based on the assumption that a woman cannot be pregnant during that interval. This "rule" is only a suggestion to decrease the probability of unsuspectingly exposing a developing embryo or fetus. The idea has been popular in some medical centers in Great Britain but not in the United States, though it has been recommended in clinical radiology.

The evidence that radiation exposures at levels of diagnostic radiology can induce cancer in the developing fetus, particularly the findings among the atomic bomb survivors,[13] remains somewhat controversial. There are a number of arguments for and against the conclusion that such low doses are carcinogenic in a fetus. However, there has been some reticence to accept a ten-day rule in clinical practice. Some radiologists have argued that such a requirement would disrupt patient scheduling in a large, busy x-ray department. Others have argued that ten days is not precise—it may be necessary to cover a 14-day period, because ovulation occurs in most women during a 14-day interval. Perhaps the most compelling argument against deferring an x-ray study of the abdomen for a period until menstruation occurs is that the condition that warranted the examination may no longer exist. It is good practice not to expose a pregnant uterus to x-rays unknowingly or unnecessarily—but if a patient is acutely ill, the benefits of the study may far outweigh the very small potential risk to an embryo.

What Can We Conclude?

In the evaluation of epidemiologic surveys and findings in laboratory animals, national and international advisory committees on radiation and health carefully review and assess the available scientific evidence for estimating the risks of the health effects in human populations exposed to low-level radiation.[4-9] The present scientific evidence and the interpretation of available epidemiologic data can draw those necessary conclusions on which to base scientific public health policy for radiation protection standards.[14] Based on the radiation risk estimates derived, any lack of precision minimizes neither the need for setting responsible public health policies nor the conclusion that such risks are extremely small when compared with available alternative options and risks normally accepted by society as the hazards of everyday life. When compared with the benefits that society has established as goals derived from the necessary activities of medical care, it is apparent that society must establish appropriate standards and seek appropriate controlling procedures that continue to assure that its health needs and services are being met with the lowest possible risks.

After a third of a century of inquiry, embodying among the most extensive and comprehensive scientific efforts on the health effects of any environmental agent, much of the important information necessary for determination of radiation protection standards is now available to decision makers for practical and responsible public health policy. It is now assumed that any exposure to radiation at low levels of dose carries some risk of deleterious health effects. However, how low this level may be, or the probability or magnitude of the risk at very low levels of dose, still are factors that are unknown and may remain so. Radiation and the public health, when it involves the public health, becomes a broad societal problem and not solely a scientific one, and to be decided by society, most often by men and women of law and government. Our best scientific knowledge and advice are essential for the protection of the public health and for the effective application of new technologies in medicine. Unless we wish to dispense with those activities that inevitably involve exposure to low levels of ionizing radiations in medicine,

we must recognize that some degree of risk to health, however small, exists.

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Specialty Conference

The 'Alice in Wonderland' Experience

Ergot Alkaloid Therapy for Prolactin-Secreting Pituitary Tumors

Discussants

RALPH C. WILLIAMS, Jr, MD; CHARLES SHERMAN, MD, *and* MAIRE T. BUCKMAN, MD

This discussion was selected from the weekly Grand Rounds in the Department of Medicine, University of New Mexico School of Medicine and Veterans Administration Medical Center, Albuquerque. Taken from a transcription, it has been edited by Drs Charles Sherman, Resident in Medicine, and Maire T. Buckman, Associate Professor of Medicine and Chief, Endocrinology Section, Veterans Administration Medical Center, Albuquerque.

RALPH C. WILLIAMS, JR, MD:* *Dr Buckman picked this title because there are many allusions throughout the different stories in* Alice in Wonderland *about the ability of Alice and her incredible imagination to make herself grow or to shrink. Dr Sherman will make the case presentation and Dr Buckman will discuss the case.*

Report of a Case

CHARLES SHERMAN, MD:† The patient is a 33-year-old man who lives in Albuquerque, is a heavy equipment operator and is married and has three children. He has a known medical history of left cryptorchidism, diagnosed first on a routine United States Navy entrance examination and treated with left orchiectomy in 1967; a vasectomy in 1974, and essential hypertension that was diagnosed in 1981 and treated with salt restriction, weight reduction, diet and a combination of triamterene and hydrochlorothiazide (Dyazide).

He was first seen by a local urologist in November 1979 for treatment of impotence. The history of this medical problem dated back to 1975 and his major symptoms were erectile dysfunction and decreased libido. He was examined and told that the cause of his impotence was most likely psychosomatic. Unhappy with this explanation, he sought further consultation with a local endocrinologist in December 1979. At that time he gave an additional history of five years of frontal headaches and symptoms of hypothyroidism: constipation, weight gain, dry skin and decreased sweating. Workup at that time included endocrine and structural studies.

Endocrine studies gave the following results: the serum testosterone level was low at 240 ng per dl (normal 400 to 1,000); serum luteinizing hormone and follicle-stimulating hormone levels were undetectable. These findings were compatible with a diagnosis of hypogonadotropic hypogonadism. Serum prolactin concentration was greatly elevated at 200 ng per ml (normal <21). A random AM serum adrenocorticotropic hormone (ACTH) level was within normal limits. A random growth hormone value was within normal limits. A thyroid-stimulating hormone (TSH) level was 1.5 μU per ml (normal <5), thyroxine (T_4) 3.2 μg per dl (normal 5 to 14) and triiodothyronine (T_3) resin uptake 30 percent (normal 25 to 35). These thyroid studies were interpreted as being suggestive of secondary hypothyroidism. He had a computerized tomography (CT) scan of the head at that time that was reported as suggestive of a pituitary tumor. Thus, in December 1979 he had a presumptive diagnosis of a prolactin-secreting pituitary tumor with hypogonadotropic hypogonadism and secondary hypothyroidism.

A regimen of bromocriptine mesylate, levothyroxine and testosterone injections was started. Because of persistent hyperprolactinemia, the bromocriptine dosage was progressively increased to 5 mg four times a day, which is twice the maximum Food and Drug Administration (FDA) approved dosage for treatment of hyper-

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ABBREVIATIONS USED IN TEXT

ACTH = adrenocorticotropic hormone
CT = computerized tomography
FDA = Food and Drug Administration
VAMC = Veterans Administration Medical Center

prolactinemia. He continued receiving this therapy for five months. Despite the testosterone injections his decreased libido and impotence persisted. Dissatisfied with this therapeutic regimen, he stopped taking the bromocriptine.

His case was intermittently followed during the next 14 months by a local endocrinologist and, because of increasing frustration related to his impotence, the patient sought another medical opinion—this time from Dr Buckman at the Albuquerque Veterans Administration Medical Center (VAMC) in June 1981. At that time, in addition to the impotence he also noted increased emotional lability. He stated that he had a "short fuse" that manifested itself both at home and at work. His alcohol intake included a shot of whiskey with breakfast and one to two cases of beer a week.

On physical examination he was a well-developed, well-nourished man who appeared stoic in nature. The rest of his examination results were remarkable for a blood pressure of 140/82 without orthostatic changes. Bilateral gynecomastia, a small amount of serous-appearing discharge from both nipples (positive for free fat globules on oil-red-O stain), an absent left testicle and a right testicle of normal size and consistency were noted.

He was given a battery of tests to evaluate pituitary function. Prolactin secretion was evaluated by a perphenazine stimulation test. Perphenazine is a phenothiazine and as a dopamine antagonist interferes with the dopaminergic inhibitory effect on prolactin secretion. In normal persons perphenazine administration results in a well-characterized rise in serum prolactin levels.[1] In patients with prolactin-secreting tumors, there is a raised prolactin level that either fails to further increase or undergoes erratic fluctuations following perphenazine ingestion.[1] The patient had an elevation of the prolactin level throughout the test and a nonspecific fluctuation in the range of 140 to 170 ng per ml. The results of this test were interpreted as being characteristic of a prolactin-secreting pituitary tumor. ACTH and growth hormone were evaluated by an insulin tolerance test and the responses were normal. The antidiuretic hormone level was evaluated by an overnight water-deprivation test and showed normal renal concentrating ability. The thyroid-stimulating hormone reserve was not tested as the patient was receiving thyroid replacement therapy.

Structural studies included visual fields by Goldmann perimetry and a CT scan of the head. The patient had normal visual fields; the CT scan showed an intrasellar macroadenoma that measured about 14 mm in height on coronal reconstruction. The major part of the tumor was in the left side of the gland. Following these studies, the patient was given pergolide mesylate, a phase II study drug manufactured by Lilly. Pergolide is a dopamine agonist similar to bromocriptine but about 100 times more potent. The dose of pergolide has been gradually increased to 100 μg daily. He has continued on pergolide treatment for the past nine months. His course so far has been remarkable for complete resolution of his galactorrhea, impotence and emotional lability; sexual activity has returned to normal. Serum prolactin levels have been persistently in the normal range (2 to 5 ng per ml). On CT scan a significant decrease in tumor mass has been observed (Figure 1).

The patient's course has been complicated by the development of a mild, asymptomatic case of pseudotumor cerebri, which was diagnosed on routine ophthalmoscopic examination after six months of pergolide therapy. Pseudotumor cerebri is most often found in obese young women who may be taking birth-control pills or tetracycline. It is characterized by headaches, decreased visual acuity and the absence of focal neurologic findings. Papilledema is noted on funduscopic examination; cerebrospinal fluid pressures are borderline or raised, with normal cerebrospinal fluid composition. On a routine follow-up examination six months after initiation of pergolide therapy, the patient was found to have blurring of his optic discs nasally, absent venous pulsations and borderline cerebrospinal fluid pressures by lumbar tap. The pathophysiology of pseudotumor in this patient is unknown. Because of the modest abnormality and the absence of symptoms, we elected to continue pergolide therapy in conjunction with frequent close follow-up with Dr Carlow, a neuro-ophthalmologist. The papilledema has been unchanged in the past three months.

Discussion

MAIRE T. BUCKMAN, MD:* There are several aspects of this case that merit in-depth discussion. Because of time constraints, however, I am going to focus on only two aspects of this patient's many problems and how they were influenced by pergolide therapy. First, there is the issue of an ergot alkaloid-induced decrease in prolactin-secreting pituitary tumor mass, which has been a subject of intense interest during the past few years; second, there is the issue of changes in emotional state following ergot alkaloid therapy, which has received relatively little attention.

Before embarking on these explorations, a brief historical review of the ergot alkaloids will help put the clinical application of these drugs in perspective.

Ergot Alkaloids

Ergot compounds have a diabolic character. They have played an important historic role in inflicting suffering, destruction and death on mankind and, more recently, in inducing beneficial pharmacologic effects.[2]

Ergot is the product of a fungus, *Claviceps purpurea,* that grows on rye and other grains. Ergot alkaloids are

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but one of numerous products identified in ergot. As early as 600 BC on an Assyrian tablet the ergot contamination of grain was described as a "noxious pustule in the ear of grain." Several hundred years later it was stated in the sacred book of the Parsees (about 400 to 300 BC) that "among the evil things created by Angro Maynes are noxious gasses that cause pregnant women to drop the womb and die in childbirth." The Greeks and Romans did not allude to this agent because they refused to eat rye; they objected to the "black and malodorous product." It was not until the Christian era that rye was reintroduced into southwestern Europe and its properties became known and recorded.

During the Middle Ages the first written descriptions of ergot poisoning, or ergotism, appeared. The overwhelming symptomatology was that of a malignant gangrenous process. Limbs were said to be consumed by the "holy fire," blackened like charcoal and, once mummified, fell off without loss of blood. The disease was called either the "holy fire" or "St Anthony's fire." St Anthony was the saint to whose shrine afflicted pilgrims traveled in search of a cure. After a long journey to the shrine, symptoms often improved; relief probably occurred because during the journey the pilgrims had consumed a diet that was free of contaminated grain. In 1670 ergot was identified as the cause of the destructive epidemics that had raged uncontrolled for centuries.

Before ergot was identified as the cause of "St Anthony's fire," it was known to have therapeutic use as

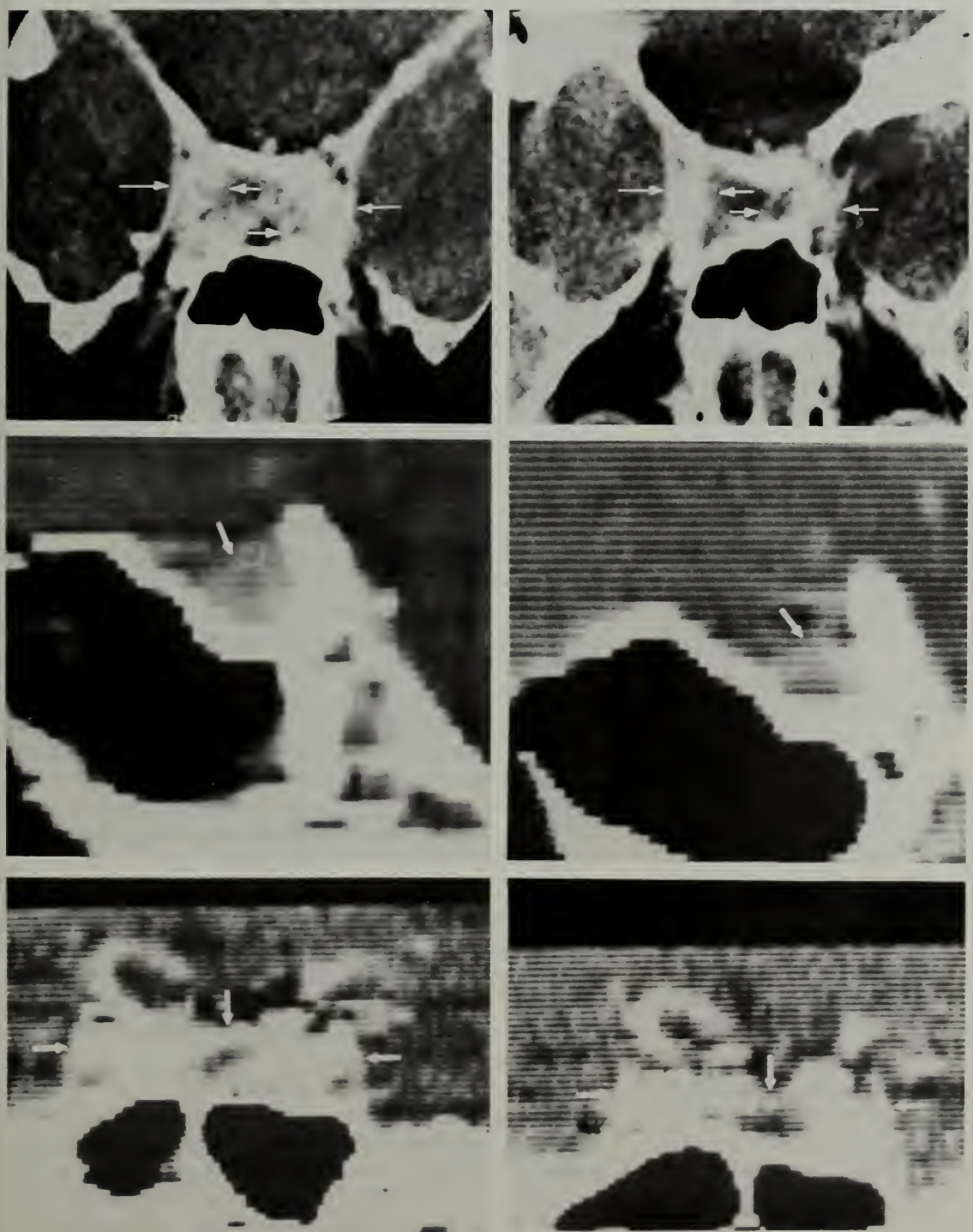

Figure 1.—Computerized tomography scan before **(left panels)** and after **(right panels)** six months of pergolide therapy. Upper panels show the axial views of the pituitary fossa containing a large tumor mass. Middle and lower panels show the sagittal and coronal reconstructions, respectively. The arrows indicate tumor boundaries. Substantial regression in tumor size in all three dimensions is evident after six months of pergolide therapy.

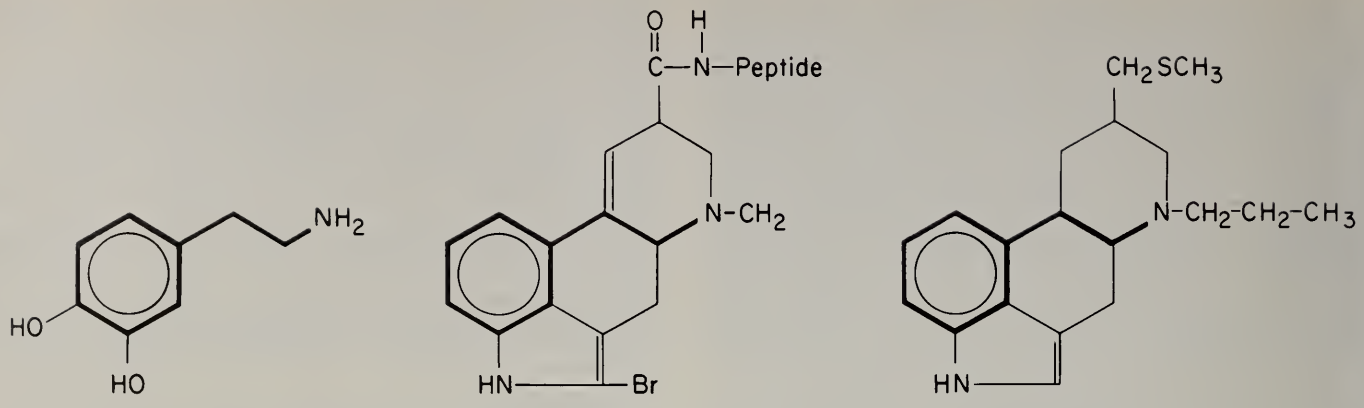

Figure 2.—Structural similarities **(heavy lines)** among dopamine, bromocriptine and pergolide.

an obstetric herb. Midwives found that its judicious administration enhanced childbirth. In 1824, however, it was observed in the United States that there was a rise in the number of stillbirths when this agent was used. As a consequence, it was recommended that drug use be restricted to the postpartum period.

The first crystalline isolation from ergot of an alkaloid that was pharmacologically active occurred in 1906. This material was identified as ergotoxine, which is actually a combination of four naturally occurring alkaloids—ergocristine, ergocornine, α-ergocryptine and β-ergocryptine. In 1920 ergotamine, the first pure alkaloid, was identified.

The application of ergot alkaloids to the field of endocrinology is a recent development. In 1954 Shelesnyak[3] observed that administration of certain ergot alkaloids suppressed decidual formation in rats and he presumed this to be related to inhibition of a pituitary "secretion" with "lactogenic activity." In 1962 Zeilmaker and Carlsen[4] observed that ergocornine administration to lactating rats inhibited milk production. Fluckiger and Wagner[5] subsequently proceeded with a systematic pharmacologic study of ergot alkaloids that led in 1968 to the development of the semisynthetic bromocriptine (2-bromo-α-ergocryptine) mesylate (Parlodel). Bromocriptine has been used clinically in hyperprolactinemic syndromes in Europe since the early 1970s. In America, however, it has only been available by FDA approval for the past four years. Pergolide mesylate, a new drug administered to our patient, is a synthetic ergoline derivative that is about 100 times more potent and three to four times longer acting than bromocriptine. It is currently in a phase II study program.

Effects of Dopaminergic Ergot Derivatives on Pituitary Prolactin Secretion

Both bromocriptine and pergolide share structural similarities with dopamine (Figure 2). Dopamine (3,4-dihydroxyphenylethylamine) is a substituted benzene ring with an aliphatic side chain. It is known to be a central nervous system neurotransmitter that suppresses pituitary prolactin secretion and may, in fact, be a physiologic prolactin-inhibiting factor.

Levodopa, a dopamine precursor, was the first drug to be used clinically in the treatment of hyperprolactinemia. Although levodopa was effective in suppressing serum prolactin concentrations, its use was limited because of its short duration of action (four to six hours), high incidence of side effects and rebound phenomenon that resulted in transient higher serum prolactin concentrations at four to six hours than before drug administration.

Bromocriptine and pergolide share with levodopa the dopamine-agonist effect of suppressing pituitary prolactin secretion. Furthermore, in a clinical setting both drugs are superior to levodopa, primarily because of their longer duration of action (bromocriptine, 6 to 12 hours; pergolide, 24 hours) and better tolerance. Bromocriptine is administered orally two to four times a day and pergolide orally in a single daily dose.

What Makes Alice Shrink?

The phenomenon of contraction and expansion (of pituitary tumors in our case) is described in Lewis Carroll's *Alice in Wonderland* with precision and clarity. Alice is a fascinating little girl. She finds herself expanding to a height of nine feet and shrinking to a mere nine inches, depending on a series of unrelated voluntary activities. She shrivels from nine feet to two feet following the seemingly harmless gesture of fanning herself with a fan dropped by the frightened White Rabbit. In John Tenniel's famous illustration entitled "The Dodo Solemnly Presented the Thimble [to the two-feet tall Alice]," the ceremony takes place in the presence of a variety of bedraggled feathered birds and dripping wet, cross and uncomfortable furry animals—all seemingly puzzled endocrine consultants trying to understand and explain Alice's contraction process. The diversity of species depicted here surely reflects the diversity of opinion regarding the pathophysiology of her diminished stature.

Like Alice, human prolactin-secreting pituitary tumors can be made to shrink—big at one time and then small at another—which is what happened to our patient's pituitary tumor. The contraction process was triggered not by a magical fan but by pergolide therapy.

Published findings confirm the ability of ergot deriva-

Figure 3.—Computerized tomography scans of a tumor of the sella turcica in a patient receiving bromocriptine, 2.5 mg 3 times a day. **Left,** A midline tomogram taken during metrizamide cisternography 12 months after initiation of treatment. There is extension of the chiasmatic cistern downward into the pituitary fossa **(arrows),** showing a partially empty pituitary fossa. **Middle,** A midline tomogram taken during air cisternography a month after withdrawal of bromocriptine therapy. There is again extension of the chiasmatic cistern downward into the pituitary fossa **(arrows),** but the degree of cisternal herniation is less than that seen after a year of treatment. **Right,** A midline tomogram taken during air cisternography 6 weeks after reinstitution of bromocriptine therapy. There is once again extension of the chiasmatic cistern downward into the pituitary fossa **(arrows),** with the degree of cisternal herniation approaching that seen after a year of receiving therapy. (Reproduced with permission from Thorner MO et al.[21])

tives to effectively shrink pituitary tumors. Quadri and colleagues[6] in 1972 reported inhibition of ectopic pituitary tumor growth in rats given ergocornine or ergonovine. Subsequent to this animal study, in the late 1970s a group of British investigators observed that reduction of pituitary tumor size in humans could also be achieved with dopamine-agonist drug therapy.

In a recent representative study, Chiodini and coworkers[7] studied 29 patients who had macroprolactinoma to whom they administered the dopamine agonists bromocriptine and lisuride (another dopamine agonist available in Europe but not here) separately or together for 1 to 50 months. Serial CT scans showed decreased tumor mass in 18 (62 percent) patients following drug therapy. Visual field defects improved or reverted to normal in 8 of 13 (62 percent) patients. Plasma prolactin concentrations decreased in all patients and returned to normal levels in 15 (52 percent). In two patients serum prolactin was observed to return to normal levels even though tumor size was unchanged after 15 to 16 months of drug therapy. Tumor mass reduction has been reported as early as after two to three weeks of treatment, or it may take many months. In no patient has an increase in a benign tumor mass been reported during dopaminergic drug therapy, suggesting that tumor growth may be retarded even when no regression is observed. Unfortunately, complete regression of macroadenomas has not been documented. Thus, dopamine-agonist therapy is useful in treating prolactin-secreting pituitary tumors to retard tumor growth or, optimally, to effect a decrease in tumor mass. Drug-induced shrinkage of prolactin-secreting pituitary tumors has now been reported in more than 60 patients.[7-21]

What Makes Alice Expand?

Alice taught us that where there is the potential for contraction, there is also the potential for expansion. Indeed, prolactin-secreting tumors may expand when drug therapy is discontinued.

Thorner and associates[21] reported the cases of two patients in whom tumors were observed to show the Alice-in-Wonderland phenomenon. In one patient, a month after bromocriptine therapy was stopped, an increase in tumor size was observed when compared with the size of the tumor after 12 months of drug treatment. Following reinstitution of drug therapy, the tumor once more regressed (Figure 3). In spite of unequivocal evidence of tumor regression, serum prolactin levels never returned to normal in this patient; however, prolactin concentrations did roughly parallel changes in tumor size. This study showed expansion and contraction of tumor mass, depending on dopamine-agonist administration or withdrawal. Clinicians need to be cognizant of the possibility of the expansion aspect of the Alice-in-Wonderland phenomenon when medically treating patients who have macroadenoma.

Understanding of the mechanism of ergot alkaloid-induced regression of tumor mass is limited. MacLeod and Lehmeyer[22] showed that certain ergot alkaloids inhibited both release and synthesis of prolactin from rat pituitaries in vitro. Furthermore, daily administration of a variety of ergot alkaloids to rats bearing ectopic prolactin-secreting tumors strikingly inhibited tumor growth.[6,22] An antimitotic effect on normal rat pituitary lactotropes has also been found.[23] Consonant with the antimitotic effects of ergot alkaloid treatment, decreased DNA synthesis has been shown in bromocriptine-treated rat pituitaries.[24] The mechanism of dopamine-agonist-mediated inhibition of DNA synthesis is unknown and warrants further investigation.

Effect of Dopaminergic Ergot Derivatives on Psychologic Factors

Our patient had diminished libido and impotence as the major presenting symptoms of his prolactin-secreting pituitary tumor. These symptoms are clearly related to hyperprolactinemia.[25] He also had emotional lability. During the past ten years of treating patients with prolactin-secreting pituitary tumors, I have heard numerous testimonials regarding major changes in behavior, personality and emotional well-being following restoration

of normoprolactinemia. Frequently there was no specific psychologic distress mentioned at the time of the initial evaluation; however, following successful restoration of euprolactinemia, patients and often family members would voluntarily report an important change: less irritability, improved mood, "nicer" personality and so forth. To define the nature of the psychologic distress and quantitate the changes, I have done a study with Dr Robert Kellner, Department of Psychiatry (University of New Mexico School of Medicine), using a variety of psychologic self-rating scales.

Before embarking on a description of the clinical observations, a brief review of the findings from studies with animals is appropriate. Prolactin influences behavior patterns of numerous animal species, especially behavior that fosters propagation and survival of the species.[26] There is conflicting information about the role of prolactin in some types of behavior, such as aggression, the prolactin influence perhaps being species specific. In a mouse species, *Peromyscus leucopus,* the females are aggressive during all reproductive states. A recent study in this species suggests a link between prolactin and aggressive behavior. Gleason and associates[27] examined the number and duration of aggressive acts towards other mice following a period of isolation (Table 1). In a proestrous female mouse there were relatively few aggressive acts and the duration was relatively short. This changed dramatically when the animal lactated and nursed her young. On the other hand, when oophorectomies were done on the animals, there was a profound decrease in both aggressive parameters compared with normal proestrous animals. Because estrogen is a major regulator of prolactin secretion, oophorectomy associated with decreased estrogen results in diminished serum prolactin level, which may be responsible for inhibiting aggression. To test this possibility, prolactin was administered to the animals that had had oophorectomies. Administration of prolactin resulted in a dose response-related increase in the number and duration of aggressive acts. Teleologically, it is reasonable that lactation should be associated with enhanced aggressive behavior to protect the young. This study indicates that prolactin may be associated with aggressive behavior in this mouse model.

TABLE 1.—*Measures of Aggressiveness in Cycling or Lactating Female* Peromyscus leucopus *and Ovariectomized (OVX) Females Injected With Vehicle or Prolactin (PRL)**

Experimental Group	*Number of Aggressive Acts*†‡	*Duration of Aggressive Acts*†‡ *(sec)*
Proestrous female	5.7 ± 1.8^1	8.9 ± 4.2^1
Lactating female	11.8 ± 2.1^2	147.2 ± 18.7^2
OVX+vehicle	0.9 ± 1.1^3	0.1 ± 1.3^3
OVX+100 μg PRL	3.8 ± 1.7^1	13.2 ± 6.4^1
OVX+200 μg PRL	10.2 ± 2.0^2	104.6 ± 15.8^2
OVX+400 μg PRL	18.4 ± 1.9^4	468.0 ± 35.9^4

*Reproduced with permission by Gleason PE et al and Behav, Neural Biol.[27]
†Mean±SEM.
‡Means in one column with same superscript are not different; analysis of variance, followed by Scheffé test, $\alpha = .05$.

A few studies in humans have also suggested that prolactin may influence behavior. Hyperprolactinemia was found to be associated with high levels of anxiety[28] and depression[29] in two uncontrolled studies. Fava and co-workers[30] compared psychologic parameters in hyperprolactinemic, amenorrheic women and euprolactinemic, amenorrheic women. They found significantly more depression, hostility and anxiety in the hyperprolactinemic group compared with either the euprolactinemic, amenorrheic women or a control group (Table 2). This study suggests that although amenorrhea per se is associated with psychologic distress, hyperprolactinemia accentuates the symptoms substantially.

To further investigate the relationship beween prolactin and psychologic distress, Dr Kellner and I conducted a double-blind simple crossover study of placebo versus bromocriptine in eight hyperprolactinemic patients.[31] Each treatment protocol lasted six weeks. Five psychologic self-rating scales were administered at intervals throughout the study: (1) the Beck Depression Inventory, (2) the Symptom Rating Test, (3) a symptom questionnaire, (4) a relative five-point global self-rating scale of distress and (5) an absolute self-rating scale of libido. All patients had sustained hyperprolactinemia with either proved (by surgical procedure or CT scan) or presumed (prolactin unresponsiveness following perphenazine administration) pituitary tumors. In addition, they had symptoms of hyperprolactinemia that included menstrual dysfunction, infertility, galactorrhea and hirsutism.

Results of this study show that hyperprolactinemic patients suffer from psychologic distress similar to that seen in psychiatric outpatients (Table 3). Reduction of distress was observed following a decrease in serum prolactin concentrations with bromocriptine treatment. Scores improved significantly on 9 of 11 parameters examined (higher scores correlate with more distress), indicating lessened symptoms of anxiety, de-

TABLE 2.—*Kellner Symptom Questionnaire Scores in Patients With Hyperprolactinemia and Amenorrhea (Group A), Amenorrhea Only (Group B) and Normal Controls (Group C)**†

	Group A n=10		*Group B n=10*		*Group C n=10*		*Significance of Difference*		
	$\bar{x}$	*SD*	$\bar{x}$	*SD*	$\bar{x}$	*SD*	*A/B*	*A/C*	*B/C*
Anxiety	12.8	4.7	7.9	4.0	3.4	2.4	$P<.01$	$P<.001$	$P<.05$
Depression ...	13.0	4.0	7.6	2.4	3.0	2.5	$P<.001$	$P<.001$	$P<.01$
Somatization ..	10.1	5.3	11.6	6.6	2.8	2.0	NS	$P<.01$	$P<.01$
Hostility	8.8	4.6	3.7	1.9	2.5	1.9	$P<.001$	$P<.001$	NS

*Female hospital employees matched for age and social class.
†Reproduced with permission by Fava G et al and Psychother Psychosom.[30]

TABLE 3.—*Scores on Self-Rating Scales Following Placebo or Bromocriptine Treatment**

	Placebo ($x \pm SD$)	*Bromocriptine* ($x \pm SD$)	*F value*	*P*
Serum Prolactin ...	81.9±56.4	21.4±17.1	38.5	<.001
BDI Depression ..	14.8±13.1	3.6± 4.1	4.5	NS
SRT Anxiety	4.5± 3.7	2.0± 1.9	6.1	<.05
Depression ..	6.3± 4.5	2.5± 2.7	6.1	<.05
Somatic	5.1± 3.3	2.4± 1.9	6.6	<.05
Inadequacy ..	5.9± 3.6	2.1± 2.2	8.5	<.05
SQ Anxiety	8.3± 6.6	3.0± 4.5	7.8	<.05
Depression ..	8.6± 5.0	2.9± 3.9	9.3	<.025
Somatic	13.5± 4.6	8.8± 3.6	6.3	<.05
Hostility	10.3± 6.0	4.6± 4.8	6.4	<.05
Global distress	3.8± 1.0	1.9± 1.1	7.4	<.05
Libido	2.6± 1.8	1.4± 0.5	4.9	NS

BDI=Beck Depression Inventory; SRT=Symptom Rating Test; SQ=Symptom Questionnaire; NS=not significant.

*Reproduced with permission of The Endocrine Society Program and Abstracts 64th Annual Meeting.[31]

pression, hostility and somatic problems. Libido was likewise enhanced with bromocriptine treatment, but the difference did not reach a statistically significant level. Although an independent drug effect cannot be excluded in this study, in the context of the other data discussed above, the results are suggestive that hyperprolactinemia may negatively influence psychologic well-being.

Summary

The development of new ergot alkaloid derivatives with dopamine-agonist activity has had a major impact on the treatment of human prolactin-secreting pituitary adenoma. Akin to Alice's experiences in *Alice in Wonderland,* the tumors have been shown to contract and expand on administration or withdrawal of dopamine-agonist drugs. Although medical therapy does not appear to be curative for macroprolactinoma at this time, it does offer an alternative or adjunct to other modalities of therapy. Research regarding optimal dosage, timing and duration of therapy—as well as possible development of newer and better drugs—may yield yet more optimistic results in the future. For the time being, dopamine-agonist drugs offer a potent palliative alternative and adjunct to surgical and radiation therapy.

A few studies have suggested that hyperprolactinemia may be associated with significant psychologic distress. Attention to assessment of the psychologic state in hyperprolactinemic persons may uncover significant symptomatology that may benefit from dopamine-agonist treatment independent of other indications for such therapy.

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Medical Staff Conference

Donor-Specific Blood Transfusions

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR SMITH:* *The topic in this Medical Staff Conference on renal transplantation and the recent advances that have occurred in that form of treatment is that of the donor-specific blood transfusions. The discussant is Dr Oscar Salvatierra, Professor of Surgery and Urology and Chief of the Transplant Service.*

DR SALVATIERRA:† The ultimate objective of renal transplantation is to obtain maximal graft and patient survival. Of all the therapeutic innovations introduced in kidney transplantation, pretransplant blood transfusions are probably the simplest, safest and most cost effective in improving the outcome for transplant recipients. The most attractive aspect of transfusion therapy is that it improves graft survival without concomitantly suppressing the immune response to infectious organisms. Opelz and colleagues[1] initially reported in 1973 that pretransplant blood transfusions were associated with improved graft survival in cadaver transplantation. Since then, studies from many centers have confirmed the beneficial effects of blood transfusions in cadaver transplantation.

Of particular interest, however, have been the results achieved with the donor-specific blood transfusion protocol introduced at the University of California, San Francisco, in 1978.[2] This protocol for the deliberate pretransplant transfusion of blood from a prospective kidney donor to a prospective kidney recipient was initiated in an attempt to select potentially successful transplants from mixed-lymphocyte-culture-incompatible, related donor-recipient pairs and to perhaps alter the recipient immune response.

Only a few prospective transplant recipients have an ideally compatible related donor with good graft survival expectations, such as a sibling with identical human leukocyte antigens or a one-haplotype sibling or parent-child with a minimally reactive mixed-lymphocyte culture. Most prospective transplant recipients will have a one-haplotype match with a highly reactive mixed-lymphocyte culture and the results in this group at our and other centers have been no better than those obtained with cadaver transplantation. A highly reactive, two-way mixed-lymphocyte culture with a stimulation index of greater than seven has formed the primary entry criterion to our protocol of deliberate donor-specific blood transfusions before living-related renal transplantation.

The rationale for our trial was based on multiple factors, both experimental and clinical. Past studies done on animals have shown as far back as 1964 that prolonged renal allograft survival could be obtained by actively conditioning a host with fresh donor blood at varying intervals before organ grafting.[3] Because donor blood transfusions given to recipients before renal allografting might result in sensitization to the donor and subsequent hyperacute rejection, clinicians had previously been very hesitant to use this technique in human renal transplantation.

I would like to briefly describe the donor-specific blood transfusion protocol and indicate the outcomes from donor-specific transfusion in those persons receiving a kidney from their blood donor. I will also describe the specific risk of sensitization to a potential kidney donor and the sensitization that might result to a panel of 30 unrelated donors. These findings have recently been presented at the IXth International Congress of the Transplantation Society in Brighton, England.[4]

Description of Protocol

The protocol itself involves transfusion of 200 ml of fresh whole blood or packed-cell equivalent three separate times at two-week intervals.[2,5] The sensitization of the potential kidney recipient is closely moni-

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Refer to: Salvatierra O Jr: Donor-specific blood transfusions—Medical Staff Conference, University of California, San Francisco. West J Med 1983; 138:398-402.

tored against blood donor lymphocytes by donor-specific crossmatch testing of stored weekly recipient sera two to three weeks after receiving the last donor-specific blood transfusion and immediately before transplantation. Criteria for proceeding with transplantation have included negative results from the T-warm and B-warm donor-specific crossmatch test. In the first 144 patients, the same weekly sera collected from the donor-specific transfusion recipient have also been screened against a random panel of 30 unrelated donor lymphocytes for T-warm, B-warm and B-cold panel cytotoxic antibodies.

Through mid-1982, 172 patients have received blood from their prospective kidney donor before the proposed transplant. Most of these patients (157) were potential recipients of first kidney grafts, and in this group 70 percent had a negative donor-specific crossmatch following a donor-specific blood transfusion. In a smaller group of 15 patients who were potential

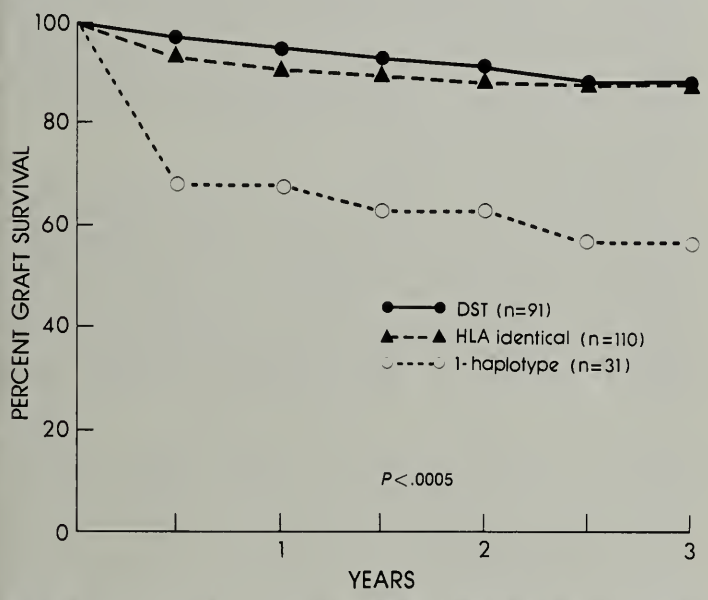

Figure 1.—Survival of living, related grafts since 1978, when the donor-specific blood transfusion (DST) protocol was initiated. HLA = human leukocyte antigen.

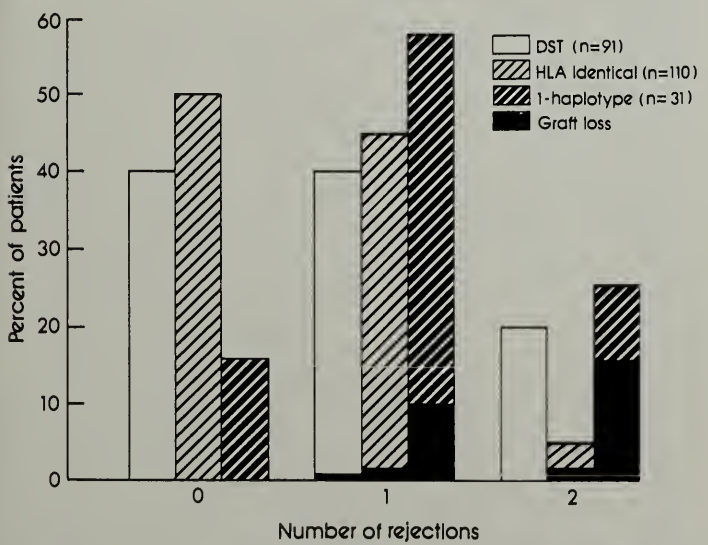

Figure 2.—Incidence of rejection episodes through the first three months following related transplantation done since 1978. DST = donor-specific blood transfusion, HLA = human leukocyte antigen.

recipients of a second or third transplant, only 33 percent had a negative donor-specific crossmatch following the donor-specific blood transfusion protocol. These patients exemplified a group of established responders already having lost a previous transplant. From the group of patients with a negative donor-specific crossmatch, 103 have subsequently received a kidney from their blood donor. The mean mixed-lymphocyte-culture stimulation index of this group was high, and most of these patients were a one-haplotype match. However, with the success of the protocol we have recently included four zero-haplotype donor-recipient pairs.

Comparison With Other Transplant Patients

I would like to compare the results achieved in 91 consecutive patients receiving a kidney from their blood donors and observed for a minimum of three months with the results from other living-related categories of patients concurrently having received transplants since 1978, when this protocol was initiated at our center. The latter include 110 patients in the group whose donor has identical human leukocyte antigens and 31 in the one-haplotype group that were not given the donor-specific blood transfusion protocol. The patient profile for these three living-related categories is essentially the same, except that those receiving the kidney from their blood donor had a higher incidence of type I (insulin-dependent) diabetes (27 percent) and included a greater number of children (17 percent). In addition, the mixed-lymphocyte-culture stimulation index in the donor-specific transfusion group was the highest—20.1 compared with 1.2 in the group that has identical human leukocyte antigen and 7.9 in the one-haplotype non-transfusion group.

Graft survival in these three living-related categories of patients is shown in Figure 1. Graft survival in the donor-specific transfusion group was 94 percent at one year, 91 percent at two years and 87 percent at three years. Graft survival in the group that has identical human leukocyte antigens—the supposed immunologic privileged group wherein we find the best graft survival in human renal transplantation—was 90 percent, 87 percent and 87 percent, and graft survival in the one-haplotype non-transfusion group was 67 percent, 62 percent and 56 percent at one, two and three years, respectively.

We should not only look at graft survival, we should also attempt to assess the posttransplant course of these recipients; this is perhaps best done by analyzing the incidence of rejection episodes in these living-related categories. Figure 2 depicts the incidence of rejection episodes through the first three months after transplantation and the incidence of graft loss following treatment of these rejection episodes. These living-related graft groups are categorized according to whether they had no, one or two rejection episodes. The percentage of patients with no or one rejection episode was essentially similar in the donor-specific transfusion group and the group whose donor had identical human leukocyte antigens. The one-haplotype non-transfusion group has a

smaller percentage of patients without any rejection episodes.

Most patients with rejection episodes in the donor-specific blood transfusion group and the group with identical human leukocyte antigens were successfully treated and had a low rate of graft loss. However, in the one-haplotype non-transfusion group, 17 percent of those patients with a first rejection lost their graft, whereas 67 percent of those with a second rejection had graft loss. The mean serum creatinine levels in patients with functioning grafts in the three living-related categories are shown in Table 1. The donor-specific transfusion group showed satisfactory mean creatinine levels through three years, as did the group with identical human leukocyte antigens. In the one-haplotype group that did not have donor-specific transfusions, there is a slight trend upward of serum creatinine levels towards the third year.

TABLE 1.—*Mean Serum Creatinine Values in Patients Who Had Functioning Grafts*

Donor Category	Duration of Graft Survival				
	3 Months mg/dl	*6 Months mg/dl*	*1 Year mg/dl*	*2 Years mg/dl*	*3 Years mg/dl*
Donor-specific blood transfusions (DST)	1.4	1.5	1.6	1.4	1.0
HLA-identical	1.5	1.5	1.4	1.3	1.3
One-haplotype, non-DST	1.3	1.5	1.5	1.7	1.8

HLA = human leukocyte antigen.

TABLE 2.—*Patterns of Donor-Specific Sensitization Using Crossmatches of 57 Recipients*

	Initial Appearance of Donor-Specific Crossmatch		
	After First DST	*After Second DST*	*After Third DST*
T-warm (n=27)	10	9	8
B-warm converting to T-warm (n=15)	4	4	7
B-warm (n=15)	6	4	5
Percent of Total	35	30	35

DST = donor-specific blood transfusion.

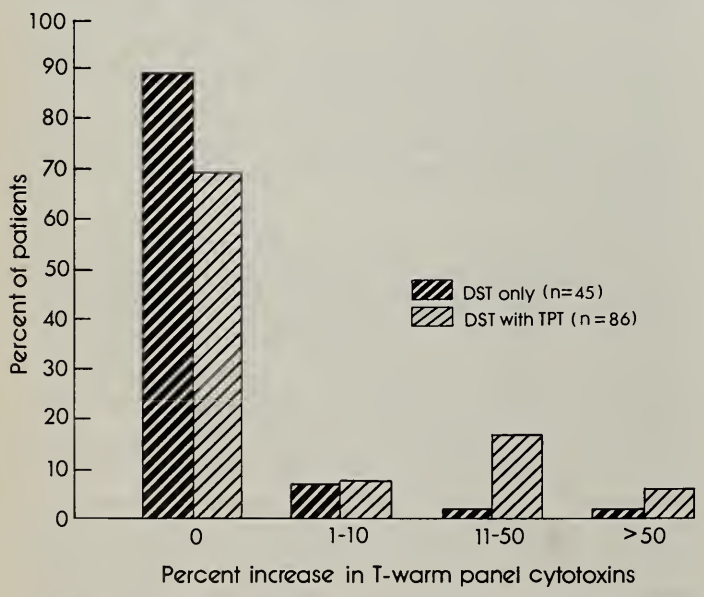

Figure 3.—Influence of third-party blood transfusions (TPT) on T-warm panel sensitization in patients with donor-specific blood transfusion (DST) before primary transplantation.

This protocol has been particularly beneficial for pediatric patients and diabetic patients. In pediatric patients there is significant growth retardation with the development of uremia. Restoration of normal growth rates can for the most part be achieved only with a successful transplant. The donor-specific blood transfusion protocol has allowed earlier transplantation in these children, with restoration of normal growth rates. In patients who have juvenile diabetes, cadaver transplantation has provided less-than-optimal success and yet a successful transplant is the desired therapy for a diabetic patient. With a diabetic patient there is expected medical exclusion of some family members, so that there is a lesser opportunity to identify an ideally compatible related donor within that family. It is here that the donor-specific transfusion protocol has provided successful transplants from donors among previously unacceptable, incompatible family members.

Patterns of Sensitization

I would now like to briefly review the antibody patterns that occur after donor-specific blood transfusion, looking at the antibodies produced to a specific blood donor and assessing the antibodies produced to a random panel of 30 unrelated donors.[6] In regards to antibodies produced to a specific blood donor, there are three patterns of donor-specific sensitization (Table 2). About half of those in whom a positive crossmatch develops will have a positive T-warm pattern. About another one fourth will have an initial positive B-warm pattern, later converting to a positive T-warm pattern. There will be another one fourth who will have only a persistent B-warm pattern. There was an essentially equal distribution of the initial appearance of any positive crossmatch pattern after the first, second and third donor-specific transfusions.

Panel sensitization should be analyzed for two reasons: (1) to better assess the specificity of the sensitization that might develop after exposure to repetitive transfusions from one's potential kidney donor and (2) to assess whether a patient in whom a positive crossmatch develops following donor-specific transfusion might possibly become untransplantable. In other words, by also evaluating the extent of cytotoxicity to a panel of 30 unrelated donors, one can assess the chances of identifying a subsequent crossmatch-negative compatible cadaver (unrelated) graft. Figure 3 shows the percent increase in T-warm panel cytotoxins in the group of patients who received donor-specific transfusion protocol only, and in the other group of patients who, along with the donor-specific transfusion, also had third-party transfusions for medical reasons. In only 4 percent of the patients who had donor-specific transfusions alone did a more than 10 percent increase in T-warm panel cytotoxins develop, compared with 23 percent in the group that received donor-specific and

third-party transfusions ($P=.01$). Third-party transfusions were erratic and in the patients who received them, neither the number nor timing of third-party transfusions influenced the rate of sensitization. Only the absence of any third-party transfusion history was significant. This indicates that in a patient who receives donor-specific transfusions alone, the sensitization does appear to be narrow, as would be expected from exposure to a limited number of transplantation antigens. If, however, a patient is exposed to a greater variety of transplantation antigens in the form of a larger number of third-party transfusions, then there is a greater expectation of increased panel sensitization. When one looks at these groups as a whole, the mean increase in T-warm panel cytotoxins from baseline in the donor-specific transfusion group only was only 2.6 percent, whereas the donor-specific plus third-party transfusion group had a 9.5 percent increase in T-warm panel cytotoxins from baseline ($P=.01$), neither value of which was sufficient to exclude the later possibility of cadaver transplantation in any of these patients. In fact, of the group that did become sensitized to the donor-specific transfusions, a substantial number of these patients later received a transplant from a donor other than the transfusion donor. Most of these have been recipients of a primary cadaver graft. Some have received a second cadaver graft, and one patient received a kidney from a family member with a haplotype different from the sensitizing haplotype. In the cadaver group, graft survival has been the same as in the cadaver group without donor-specific transfusion from a potential related donor.

These results continue to indicate that the donor-specific blood transfusion process in itself does not appear to jeopardize the potential recipient, even those in whom a positive crossmatch to their potential related donor develops. For the potential kidney donors in the donor-specific transfusion protocol, the process of preliminary blood donation has been harmless and has spared many donors the possibility of donating a kidney that would probably later be rejected. The potential donor who then has a positive donor-specific crossmatch has experienced increased self-esteem in actively participating with their family member in the identification of a compatible kidney. For the transfusion donor eventually undergoing an operation, the process of renal donation is being accomplished with excellent prospects of success, and the donor is able to approach the surgical procedure with more confidence and less anxiety.

Possible Mechanisms

There are two possible mechanisms of the donor-specific protocol, neither of which is mutually exclusive. The first explanation, one more readily recognized, is the process of selection as the donor-specific blood transfusion protocol segregates responders from non-responders by means of the careful monitoring of the specific antibody response to the blood donor. Donor-specific blood transfusion thus appears to eliminate donor-recipient pairs with certain graft loss by specific

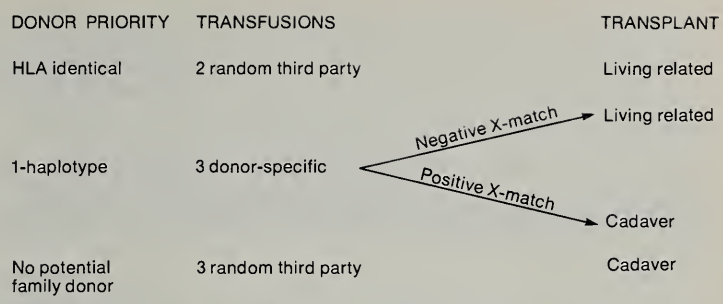

Figure 4.—Preoperative transplantation strategy indicating donor priorities.

advanced testing. However, the excellent graft survival and generally benign posttransplant course achieved in many patients who eventually receive a kidney from their crossmatch-negative blood donor evokes the need for other explanations. Because immunogenic exposure has involved repetitive transfusion of donor-specific antigens in modest doses, the induction of some degree of specific unresponsiveness to these same antigens on the subsequently transplanted kidney can be theorized. The posttransplant donor-specific transfusion effect probably encompasses a complex of various mechanisms, and it may be that suppressor cells and anti-idiotypic antibodies play an important role in this induction.

Future changes that could be made in the donor-specific blood transfusion protocol to decrease the donor-specific sensitization rate include azathioprine (Imuran) coverage during the administration of the blood transfusion, which is presently being considered at this and other centers.

Our growing experience with donor-specific blood transfusion continues to support the potential efficacy of this procedure. Additionally, other centers have now reported similar results.[7-11] Because graft survival and posttransplant course of recipients of a kidney from their blood donor appear to be similar to matches with identical human leukocyte antigens, we have started to use the donor-specific transfusion protocol for all one-haplotype matches, regardless of the mixed-lymphocyte-culture result. Because our donor-specific transfusion results have involved only highly reactive mixed-lymphocyte-culture donor-recipient pairs, it can be expected that the minimally reactive mixed-lymphocyte culture group should yield at least similar results. Figure 4 places the donor-specific transfusion protocol in the perspective of a current preoperative transplantation strategy to select the optimum donor for a potential kidney recipient electing transplantation.

In conclusion, from the results it appears that mixed-lymphocyte-culture-incompatible living-related pairs can be effectively pretreated with deliberate donor-specific transfusions. Graft survival and posttransplant course of recipients of a kidney from their blood donor appear to be similar to those with identical human leukocyte antigens. In the absence of donors with identical human leukocyte antigens, this protocol offers the best opportunity for successful transplantation, with particular impact on diabetic and pediatric patients. No

potential first allograft recipient has been made non-transplantable, and the potential benefits of the donor-specific transfusion protocol appear to definitely outweigh the minimal risks of increased panel sensitization. In addition, because the transfusion is coming from a family member with a known medical history, the risk of transmitting hepatitis has been minimal, if not quite negligible.

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Medical Practice Questions

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Constant Blood Pressure Monitoring

QUESTION:

Is constant monitoring of blood pressure, such as using the ambupress monitor, considered accepted medical practice?

OPINION:

In the opinion of the Advisory Panels on General and Family Practice and on Internal Medicine, constant blood pressure monitoring has shown potential usefulness only for carefully selected circumstances. The efficacy of this technique in routine clinical settings requires continued investigation.

Constant blood pressure monitoring is of use now primarily in research settings as part of investigational protocols. Additionally, it may have some value in selected patients in whom there appears to be disparity between casual blood pressures and end organ damage, those with borderline levels of hypertension and those with selected and relatively rare clinical conditions such as pheochromocytoma.

Previous studies indicate a great deal of variation in blood pressure throughout a 24-hour period. However, it has not yet been shown that the analysis of a 24-hour recording can successfully predict prognosis, pathological correlates or even optimal treatment strategies.

Some useful practical data have emerged in short-term monitoring. Multiple automated blood pressure readings during a 2-hour period seem reasonably predictive of the full 24-hour blood pressure average. There is promise that this 2-hour average, the subject of current investigation, could represent a reproducible and usable blood pressure measurement that would be superior to the conventional, casual single blood pressure reading.

Epitomes

Important Advances in Clinical Medicine

Psychiatry

The Scientific Board of the California Medical Association presents the following inventory of items of progress in psychiatry. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers or scholars to stay abreast of these items of progress in psychiatry that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Psychiatry of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, 731 Market St, San Francisco, CA 94103

Heterogeneity of Dementia

THE CLINICAL SYNDROME of dementia is characterized by deficits in memory, judgment, language and other cognitive functions, as well as changes in personality and behavior. It is distinguished from delirium by the presence of clear consciousness in a patient. Dementia is etiologically heterogeneous, and a physician's first responsibility is to identify those patients whose dementia is caused by disorders amenable to specific treatments—for example, drug reaction, depression, metabolic dysfunction, infection, trauma, nutritional deficiency or neoplastic processes.

Unfortunately, the most frequent causes of dementia generally lead to progressively greater mental impairment despite symptomatic treatment. A study including 422 patients admitted to hospital with a diagnosis of dementia gave the following etiologic information: dementia of the Alzheimer type, 47 percent; multi-infarct type, 9 percent; alcohol related, 10 percent; normal-pressure hydrocephalus, 5 percent; depression, 4.5 percent; central nervous system tumors, 3.5 percent; hereditary chorea (Huntington's disease), 3.5 percent; drug toxicity, 2 percent; paralysis agitans (Parkinson's disease), Creutzfeldt-Jakob disease and other causes, each less than 1 percent.

Dementia of the Alzheimer type has begun to attract the most attention. It appears to increase in frequency with advancing age and is said to account for at least 20 percent of demented patients 80 years of age and older. A cholinergic deficit has become an accepted correlate of Alzheimer type dementia and yet in a significant number of clinically diagnosed patients involvement of the cholinergic system has not been found.

In contrast to the etiologic heterogeneity of the clinical syndrome of Alzheimer type dementia, one small autopsy series reported highly significant loss of neurons in the nucleus basalis (the major source of cholinergic brain innervation) in all cases, whereas a different group reported an equally striking loss of neurons in the locus ceruleus (the major source of noradrenergic brain innervation) in another small autopsy series.

The clinical diagnosis of Alzheimer type dementia remains largely one of exclusion: computerized tomographic scans are important to rule out other causes of dementia, electroencephalographic changes tend to be confirmatory rather than diagnostic and the clinical value of positron emission tomography (PET) and nuclear magnetic resonance (NMR) scans is yet to be established. The role of various etiologic agents (infectious, toxic metals, nutritional deficiencies and the like) remains questionable. Current treatment research focuses on correcting possible neurotransmitter imbalances and maximizing the function of surviving neurons. The search for etiologically distinct subgroups has been directed toward genetic markers (for example, haptoglobins and human leukocyte antigens), chromosomal abnormalities (for example, aneuploidy and sister chromatid exchange) and deficits in host defense mechanisms involving the immunoglobulin system and the philothermal response. Many treatments have been suggested for Alzheimer type dementia; so far, only those aimed at symptomatic relief have an acceptably high level of efficacy (for example, low doses of antipsychotic drugs for paranoid or agitated behavior, or both, and low doses of antidepressants for affective or vegetative concomitants of depression). Current experimental approaches include attempts to increase cen-

tral nervous system concentrations of acetylcholine, chelating agents to lower aluminum concentrations, metabolic enhancers and treatments combining two or more approaches. None are particularly encouraging.

Patients with multiinfarct dementia may benefit from taking medications expected to reduce the incidence of further infarctions (for example, anticoagulants such as aspirin, 1¼ grains every other day), though the prophylactic efficacy of this approach has not been proved. Of course, attempts should be made to control, at least in patients with multiinfarct dementia, risk factors for cerebrovascular disease, such as hypertension and smoking.

LISSY F. JARVIK, MD, PhD
ROBERT E. NESHKES, MD

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Phencyclidine (PCP) Psychosis

THE ABUSE of phencyclidine hydrochloride (known on the street as PCP, angel dust, wack, shermans or super kools) is common, perhaps epidemic, in most urban areas. Persons who have ingested large doses either through a single exposure or frequent use can have detectable concentrations of phencyclidine in their blood for months or even years afterward. The incidence of phencyclidine intoxication in patients presenting to urban psychiatric emergency services is alarming and usually underestimated. Commonly used laboratory detection methods (gas chromatographic techniques using flame ionization) are relatively insensitive with lowest limits of 50 to 100 ng per ml, whereas a glass capillary-gas chromatographic nitrogen detector method readily identifies phencyclidine in the 5 to 10 ng per ml range. Furthermore, phencyclidine screenings are commonly done on urine samples that are usually falsely negative if the urine is alkaline (pH above 6.0) even in the presence of high blood concentrations. Using the more sensitive techniques, phencyclidine has been detected in the blood of 40 percent to 70 percent of patients presenting to a Los Angeles public hospital psychiatric emergency service.

The psychiatric features of phencyclidine intoxication are protean and atypical. The commonly ascribed symptoms—toxic psychosis with agitation, disorientation, visual hallucinations and paranoid delusions coupled with nystagmus, tachycardia and hypertension—are found in less than 20 percent of phencyclidine-positive patients and are not related to blood concentrations of phencyclidine. Instead, patients have symptoms more typical of schizophrenia and affective disorder. Prospective comparisons of persons with laboratory tests positive for phencyclidine with those with negative results show no clinical or demographic features that distinguish the two groups, except a history of phencyclidine use, which is obtained only 25 percent of the time. Optimum treatment of phencyclidine psychosis is not firmly established but involves chemotherapy appropriate to the behavioral and psychiatric symptoms and administration of ammonium chloride (0.5 grams three times a day) to acidify the urine and enhance excretion.

ROBERT E. ALLEN, MD

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Behavioral Treatment of Mild Hypertension

WITH THE RECENT PUBLICATION of the findings of major clinical trials of antihypertensive drugs, it is now considered good practice to treat mild hypertension (diastolic pressure of 90 to 104 mm of mercury) as well as more severe cases. Given that 40 million people in the United States are estimated to have mildly elevated pressures, the economic and social consequences of such treatment are enormous. On close scrutiny of the design of the trials and the interpretation of the findings, however, serious questions have been raised about the wisdom of drug therapy in mild cases, especially for those persons free of cardiovascular risk factors such as smoking or hypercholesterolemia. Drug toxicity, disturbing side effects, possible adverse effects of long-term drug use and poor adherence are additional reasons for caution.

Nonpharmacologic modes of treatment are an alternative first step in uncomplicated cases. Weight loss and sodium restriction can be effective and are indicated in many cases, but poor adherence to diets no doubt reflects strong constitutional factors and the lifelong nature of eating habits.

Behavior patterns and psychologic and social stress have been shown to play a role in hypertension. Whether fundamental changes in behavior patterns and life-style can be achieved is uncertain. Nonetheless, people can be shown how to relax, trained to lower their blood pressure levels and advised on reducing responses to stress that facilitate blood pressure reduction.

Recent studies have shown that behavioral methods such as biofeedback and the regular practice of relaxation are effective, and studies of direct comparisons between drug and behavioral treatments have found comparable pressure reductions in many cases. Studies have shown that with the use of relaxation tapes and blood pressure biofeedback methods adapted for self-use, behavioral methods can also be used effectively by persons at home, thereby facilitating regular practice and self-help in pressure reduction. Using small groups, hypertensive patients have also been taught how to manage stress more effectively. Finally, the simple pro-

cedure of daily self-recording of blood pressure is useful for many people by itself.

Large-scale studies are now in progress, but the accumulated evidence suggests that behavioral treatments may prove beneficial, cost effective and advantageous for mild hypertension. DAVID SHAPIRO, PhD

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Panic Disorders

PANIC DISORDER has been classified in the *Diagnostic and Statistical Manual of Mental Disorders, 3rd Ed.* (DSM III) as distinct from other anxiety disorders. This distinction came from compelling evidence produced by Donald Klein, MD, in the 1960s and others in the 1970s that panic disorder has a differential treatment response compared with other disorders in which anxiety is prominent.

The essential features are recurrent paroxysmal attacks of anxiety without warning or apparent reason, though certain situations—for example, driving a car, being in crowds or a supermarket—may become associated with a panic attack. There is a sudden onset of intense apprehension, fear or terror, often associated with feelings of impending death. The symptoms can involve almost all the physioanatomic systems so that patients are consciously aware of the attack, which usually lasts several minutes and, rarely, hours. Symptoms include palpitation, chest pain or discomfort, dyspnea, a choking sensation, dizziness, vertigo, faintness, a feeling of unreality (depersonalization or derealization), paresthesias, hot and cold flashes, sweating, trembling or shaking, severe anxiety with fear of dying or going crazy, a sense of losing control and the like.

Because of the complexity of symptoms, panic disorder was often diagnosed as polysymptomatic hysteria in the latter part of the 19th century. It also carried various diagnostic labels reflecting the specialty interests of the treating physicians: "cardiac neurosis," "hyperventilation syndrome," "vertigo hysterique," "hypochondriasis," "spastic colon syndrome," "anxiety neurosis" and "agoraphobia." The recent establishment of panic disorder as a disease entity by the American Psychiatric Association no doubt validates it as an entity requiring accurate diagnosis and effective treatment.

Epidemiologically, panic disorder is estimated to occur in 2 percent to 5 percent of the general population and 10 percent to 14 percent of patients in cardiology practice, with 80 percent of the patients being women. The onset is usually in the early 20s with a uniform, unimodal age-of-onset distribution. The course of the illness is often chronic and fluctuating, with 50 percent or more of the affected having some level of disability. A common complication of this disorder is the development of phobia and avoidance of the place or situation where a patient first experienced a panic attack (classical conditioning). Patients become reluctant to be alone or in public places away from home. Because the illness usually affects persons in their wage-earning years, monetary losses amount to more than $100 million a year, not to mention the costs in human suffering.

Recent studies have elicited more information on the biologic factors of this condition, in addition to the long-held psychosocial dynamic factors. These include an increased incidence of the disorder in the first-degree relatives, a higher concordance rate in monozygotic than in dizygotic twins, a unique age-of-onset distribution and a poor response to benzodiazepine antianxiety agents. In addition, the attacks are precipitated by sodium lactate administration in persons with a history of panic disorder but not in control subjects.

Psychotherapy—psychodynamically oriented, supportive or group therapy or psychoanalysis—has yielded limited results, probably not significantly different from the spontaneous remission rate. Behavioral therapy was reported to be effective for patients with a single phobia and phobic avoidance, particularly if medication prevents primary panic attacks. The pharmacotherapy is most promising with best cost-benefit ratios. All antidepressants including monoamine-oxidase inhibitors and tricyclic antidepressants, given at doses ranging from homeopathic doses to the conventional ones used for depression, have been found to be effective. The effectiveness in treating a panic disorder with antidepressants is independent of the presence of the autonomic signs of a depression.

CHING-PIAO CHIEN, MD

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Benzodiazepine Receptors

THE DISCOVERY of the benzodiazepine receptor in 1977 has important clinical implications for our understanding the utility of benzodiazepines and their potential for abuse. These receptors are located throughout the brain and elsewhere, but their locations in the brain may give some indication of the functions of these drugs. Thus receptors in the cortex may account for seizure relief, in the limbus, anxiolytic effects, in the reticular formation, muscle relaxation, and in the cerebellum, the ataxic uncoordination seen with higher doses.

Two types of receptors have been identified, denoted types I and II. Drugs that bind to type I receptors and not type II, such as triazolopyridine, selectively provide

relief of anxiety without the other effects of benzodiazepines. Although presently available benzodiazepines bind to both types of receptors, antagonist drugs have been developed that will selectively block one type of receptor. Betacarbolines selectively block type I receptors, thereby blocking the anxiety-reducing effects of benzodiazepines. These findings may help in the development of a drug that relieves anxiety without other less desirable effects or a combination of benzodiazepine and receptor type II antagonist that accomplishes the same useful function. The benzodiazepines bind better to receptors in the presence of neurotransmitter γ-aminobutyric acid (GABA) and these receptors may play a role in GABA-ergic transmissions. This may explain the profound effect of benzodiazepines on GABA-ergic transmission.

The benzodiazepine receptors may also help to explain the benzodiazepine withdrawal syndrome. The discovery of these receptors has led to the hypothesis that the body produces endogenous benzodiazepine-like compounds that have not yet been identified. Thus, if exogenous benzodiazepines are supplied, then the body's production of benzodiazepines would decrease through inhibition of the feedback loop. The body may require several weeks to resynthesize its own benzodiazepines after exogenous compounds are withdrawn, leaving the benzodiazepine receptors devoid of benzodiazepines and leading to prolonged withdrawal symptoms. Another explanation of withdrawal is that administration of high doses of diazepam produces a highly significant increase in the density of brain benzodiazepine receptors that are then left without benzodiazepines when the exogenous drug is withdrawn.

In conclusion, the discovery of the benzodiazepine receptor helps to clarify the function of these drugs, to explain the withdrawal syndrome and to provide a basis for the future development of drugs that relieve anxiety without producing undesirable effects.

EDWARD KAUFMAN, MD

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Bulimia

BULIMIA is a syndrome of recurrent episodes of rapid binge eating of high-caloric foods, usually secretively. Binges are terminated by pain, sleep, self-induced vomiting or interruption by another person. Weight gain is limited by severely restrictive diets or fasts, self-induced vomiting or use of laxatives, or, in some cases, all of these. Patients often experience weight fluctuations of greater than 4.5 kg (10 lb). They are aware that their eating patterns are abnormal and fear not being able to voluntarily stop. Depressed mood and low self-esteem are common. Bulimia is properly diagnosed only in the absence of anorexia nervosa or other physical causes. The prevalence may be as high as 5 percent among college women. There are far fewer recognized male bulimic patients. The age of onset is ordinarily in the midteens, with eating binges following attempts at caloric restriction or related to frustration and anxiety, or both. Typically, vomiting begins a year or two following severe diets and fasts, and laxative abuse begins several years later. Complications include hypokalemia and its sequelae, various gastrointestinal complaints, dental problems and parotid and sublingual gland swelling with "squirrel face." Coexistent personality problems are common. Treatment includes individual and group psychotherapy and administration of antidepressant medications when indicated. Several other classes of medication are currently being tested. Self-help groups are often beneficial.

Factors thought to contribute to the pathogenesis of both anorexia nervosa and bulimia include personality, family and as-yet-unidentified biologic factors and cultural pressures on women to be thin. JOEL YAGER, MD

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Combined Tricyclic and Monoamine-Oxidase Inhibitor Antidepressant Treatment

COMBINING TRICYCLIC DRUGS and monoamine-oxidase inhibitors in antidepressant treatment was at one time considered so hazardous that pharmaceutical companies identified treatment with one class of drug as an absolute contraindication to treatment with the other. Nevertheless, some clinicians have used the two types of drugs together ever since they first became available, and some have claimed that such combinations may work well when all else has failed.

Repeated reviews of the literature on adverse reactions have led to the same conclusion: the combination appears reasonably safe if used within certain guidelines. Severe reactions have occurred mainly when a tricyclic was added to an established course of treatment with a monoamine-oxidase inhibitor. These reactions—characterized by hyperthermia, hypertonicity, seizures and agitated delirium sometimes progressing to coma—resemble the clinical picture of overdose more closely than that of hypertensive crises or "cheese reactions" experienced by monoamine-oxidase inhibitor-treated patients who ingest tyramine or indirectly acting sympathomimetics. Such reactions have virtually never been reported when tricyclic and monoamine-oxidase inhibitor administration is started together, at low dosage, after at least a week of not taking either type of drug. Dosage should then be increased gradually for both

drugs together to a maximal dose of half that used with the single drugs.

The major indication for a trial of combined monoamine-oxidase inhibitors and tricyclic treatment is depression that has proved refractory to adequate trials of treatment with more usual approaches—such as tricyclic antidepressants alone, monoamine-oxidase inhibitor alone, electroconvulsive therapy and so forth. A clinician choosing to try combination treatment should bear in mind that whereas some uncontrolled clinical experience has suggested its effectiveness for refractory depression, none of the four controlled studies so far reported has supported any advantage for combined monoamine-oxidase inhibitor and tricyclic treatment over administration of single drugs or electroconvulsive therapy. Nevertheless, official sanctions against the use of this approach are lifting in the face of evidence for reasonable safety with proper use. Pharmaceutic companies are revising package inserts accordingly, and last year the American College of Neuropsychopharmacology adopted as its official position paper the review by White and Simpson (1981).

KERRIN WHITE, MD

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Use of Lithium Carbonate in Psychiatric Treatment

LITHIUM CARBONATE is used to treat recurrent mood disorders. It is most effective in controlling acute mania and for prophylaxis or bipolar I (mania) and bipolar II (hypomania) manic-depressive disorders, schizoaffective disorders and recurrent unipolar depression. It is less effective as a treatment for acute depression. When lithium is used to treat acute mania, relatively high serum concentrations (up to 1.8 mEq per liter) are acceptable as long as toxic symptoms are not produced. Neuroleptic medication is commonly added for the acute manic period. The use of lithium as prophylactic treatment has to be adjusted for each patient but is generally indicated for those who have two or more affective episodes within two years, those who have a history of more than three affective episodes and patients whose previous depressions had not responded quickly to antidepressants.

Prophylactic administration of lithium is not indicated after a single manic episode, but extreme care must be used to document the lack of previous manic or hypomanic episodes. It is not uncommon to have continued mood swings during the initial prophylactic treatment with lithium because its maximum prophylactic value may not occur for more than a year after onset of treatment. In most persons control can be achieved with maintenance lithium blood concentrations of 0.6 to 0.8 mEq per liter. Some persons, however, especially the elderly or organically impaired, cannot tolerate such levels, and in these cases concentrations as low as 0.3 mEq per liter may be effective. At the other extreme are some patients in whom maintenance levels as high as 1.6 mEq per liter are required.

Lithium treatment may be started in the following ways: using a large loading dose with careful subsequent monitoring of the blood concentration, giving a single 600-mg test dose with determination of a 24-hour blood concentration or starting the patient on a regimen of 600 mg a day and increasing the dose weekly after checking the blood lithium concentration. Standard lithium serum values are measured 10 to 14 hours after the last dose of lithium. The measurement of erythrocyte lithium value, as opposed to plasma or serum levels, is not commonly used in most clinical settings. Once persons have been stabilized on a particular blood concentration at a particular dose, there is little fluctuation and for uncomplicated maintenance therapy lithium levels should be checked only every four to six months.

There is no agreement among experts on laboratory tests that should be done before starting lithium treatment. Our consensus is that a pretreatment examination should include blood tests for serum creatinine and thyroid function and analysis of urine. There are no specific medical contraindications to lithium treatment (including cardiovascular disease), though in patients with cardiac disorders baseline and lithium treatment electrocardiograms should be done. Lithium has some antithyroid effects and causes hypothyroidism in a small percentage of patients. Thus, yearly thyroid function tests should be carried out, the best being the thyroid-stimulating hormone level. Hypothyroid changes are treated by administration of thyroid replacement. While lithium decreases the kidney's ability to concentrate urine, this is rarely of importance. In the absence of preexisting renal disease or evidence of renal disease while on lithium, the serum creatinine level should be checked yearly. Previous concerns about possible renal damage due to lithium are now thought to be exaggerated. Further, worries by some patients that lithium may affect "creativity" have not been substantiated.

Most persons receiving lithium have some side effects, which are usually mild and include thirst, increased urination and mild, fine, resting tremor. Subjective side effects such as nausea or gastrointestinal distress can often be relieved by using the slow-release form of lithium because peak blood concentrations after ingestion of medication are much lower with this form. Side effects of tremor are commonly treated with administration of propranolol, polyuria with hydrochlorothiazide and acne with topical antibiotics. Approximately 20 percent of patients receiving lithium have a significant weight gain of unknown cause, but it is, of course, calorie-dependent. Lithium is compatible with all other psychotropic medications, though some and possibly all neuroleptic agents raise the intraneuronal lithium level and thus may be responsible for mild toxic changes

at previously tolerated blood concentrations. Lithium can be given in combination with diuretics if blood concentrations are measured frequently during initiation and adjustment of diuretics. Lithium may increase the potential for digitalis toxicity by lowering intracellular potassium levels; thus, careful monitoring of electrocardiograms should be carried out during stabilization periods. Lithium use is contraindicated during pregnancy and for women who are breast-feeding.

ROBERT H. GERNER, MD

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Sleep Disorders Medicine: A New Subspecialty

SLEEP DISORDERS MEDICINE has recently emerged as a new subspecialty. Nearly 100 sleep disorder centers have already been established in hospitals throughout the United States. Certified sleep disorder specialists (clinical polysomnographers) drawn from pulmonary medicine, neurology, cardiology, psychiatry, psychology and other fields offer comprehensive medical and psychiatric evaluation and treatment for a wide variety of clinical problems. A few disorders are as follows.

Excessive Daytime Sleepiness

Patients with excessive daytime sleepiness (EDS) show a persistent propensity to fall asleep at times when they wish to remain awake. Two major diagnoses should be considered: narcolepsy and obstructive sleep apnea. Narcolepsy is associated with cataplexy, consisting of brief episodes of objective muscle weakness usually precipitated by emotional arousal. It is found equally in men and women and usually begins during the late teenage years and early 20s. In contrast, patients with obstructive sleep apnea have hundreds of episodes during the night when effective respiration ceases because of upper airway obstruction. It is usually associated with profound snoring and occurs most frequently in obese middle-aged men. The symptoms of excessive daytime sleepiness may be related to the metabolic and blood gas abnormalities associated with prolonged, repeated apnea. Patients with both forms of this disorder fall asleep quickly in the sleep laboratory during daytime and nocturnal recordings.

Narcoleptic patients usually enter rapid-eye-movement (REM) sleep immediately on falling asleep. Patients who have sleep apnea show numerous episodes of apnea and may have severe, life-threatening periods of hypoxemia, hypercapnea, pulmonary and systemic hypertension and cardiac arrhythmias during apneic episodes. Once the diagnosis is established, relatively successful therapies are available for both forms of sleep disorder.

Major Depressive Disorders

Most depressed patients have insomnia, though a few have hypersomnia. More recently it has been found that many depressed patients show rather specific abnormalities of sleep, including a loss of stage 4 sleep (an electroencephalographic category) and a shortened REM latency (the elapsed time from sleep onset to the first REM period). These findings have stimulated considerable research into biologic factors in affective illness. The clinical usefulness of sleep laboratory investigations of depressed patients is currently being studied in such areas as differential diagnosis, assessment of severity and prediction of response to treatment.

Impotence

The differentiation of psychogenic and organic factors is an important consideration in the management of impotent patients. Because every normal man has full erections in association with REM periods, all-night-sleep laboratory recordings of sleep and nocturnal penile tumescence provide valuable information to clinicians who must decide whether to treat a patient psychiatrically, medically or surgically. During REM periods, it is possible to measure changes in penile circumference that occur with erections and, on awakening, to measure rigidity. Patients with organic impotency show little or no evidence of an objective erection during several nights in a sleep laboratory and are candidates for a penile prosthesis or a vascular operation.

J. CHRISTIAN GILLIN, MD

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Neuroleptic Malignant Syndrome

THE NEUROLEPTIC MALIGNANT SYNDROME appears in patients being treated with antipsychotic medication and is characterized by fever, muscular rigidity, altered consciousness and autonomic dysfunction. Although the syndrome is considered rare, it is recently being reported with more frequency in the United States. Usually seen in men younger than 40 years, it has been reported in patients with various psychiatric diagnoses. Neuroleptic malignant syndrome has also been reported to occur with the administration of most major families of neuroleptic drugs, most often in therapeutic doses. It is seen less frequently with other psychotropic agents that are given either alone or in combination.

The syndrome usually resolves spontaneously when the offending neuroleptic agent is discontinued and does not always reappear when the causative agent is readministered. It is also not related to the duration of drug administration. Laboratory evaluation shows nonspecifi-

cally abnormal findings, including an elevated creatine kinase, raised liver enzyme levels and diffuse slowing seen on the electroencephalogram. No structural abnormalities in the central nervous system have been found in autopsy studies. Death occurs in 20 percent of the cases—usually due to respiratory failure—and 50 percent of these have been related to the use of long-acting phenothiazines. Other serious complications include thromboembolism, aspiration pneumonia, cardiovascular collapse, renal failure and irreversible brain damage.

The underlying causative physiologic mechanism of this disorder is unknown, but speculation relates it to dopamine blockade in the basal ganglia and hypothalamus. Predisposing factors may include organic brain disease, dehydration or physical exhaustion.

Athough there have been scattered reports of treatment success with antiparkinsonian agents, there is currently no known treatment that can reverse the syndrome in most cases. Palliative measures include cessation of administration of the neuroleptic agent and supportive medical care. Because the most effective treatment, then, is prevention, clinicians should prescribe neuroleptic medication only when the benefits outweigh the risks in a psychotic patient.

CHARLES B. SCHAFFER, MD

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Underdiagnosis of Bipolar Disorder: Causes and Implications

NUMEROUS STUDIES, especially during the past decade, have resulted in redefining the criteria for differential diagnosis of various psychiatric disorders, especially for distinguishing the major affective disorders from the schizophrenic disorders. Observations suggest, however, that clinical practice does not yet fully reflect these redefinitions, with cases of bipolar disorder, especially the manic type, continuing to be diagnosed and therefore treated as schizophrenia. The consequences of such a misdiagnosis are several and can be tragic: (1) there is greater social stigma attached to the label of "schizophrenia" than to "bipolar disorder" (manic-depressive disorder), (2) there are poorer prognostic implications of a diagnosis of schizophrenia and a more negative effect on a patient, the family and treatment personnel (that is, "Once a schizophrenic, always a schizophrenic") and (3) often treatment is with agents that are less effective and have the potential for more both short-term and long-term deleterious effects.

Multinational studies in Western Europe have established an approximate 1:1 ratio of schizophrenia to bipolar disorder among hospital admissions. This ratio was confirmed by a study in the United States and Great Britain, indicating that the actual patient types did not differ in the two countries. Various studies have shown, however, that American psychiatrists have diagnosed schizophrenia as much as 8 to 12 times as frequently as bipolar disorder. Recent data from California suggest that underdiagnosis of affective disorder relative to schizophrenia is continuing, though the trend is toward the 1:1 ratio.

Pertinent to the underdiagnosis of bipolar disorder in this country has been the adage "even a trace of schizophrenia is schizophrenia," supported by a diagnostic approach that has relied on a cross-sectional view of signs and symptoms. The *Diagnostic and Statistical Manual of Mental Disorders, 2nd Ed,* which was in use until 1980, used such slice-in-time descriptions and additionally required that for a diagnosis of affective reaction any disturbance of thought or behavior must be consonant with the primary disorder of mood. Therefore, the presence of any mood-incongruent psychotic features excluded the diagnosis of an affective disorder. Subsequent to this edition, research has clarified the nonspecificity of many of the "schizophrenic" symptoms, including mood-incongruent hallucinations and delusions, thought disorder and catatonia. The entire range of "schizophrenic" symptoms has been noted in 20 percent to 50 percent of both manic and depressed patients. The presence or absence of affective symptoms, the family history (for schizophrenia and affective disorder particularly), the premorbid personality and the course of illness are more specific diagnostic indicators. Age of onset is not the differentiating criterion once thought; it is now recognized that bipolar disorder can occur in childhood and adolescence and that such cases tend to have a higher genetic loading and a less favorable course.

The third edition of the above-mentioned manual, now in use, provides specific diagnostic criteria, rather than cross-sectional descriptions, and incorporates many of the findings of recent research in the criteria for distinguishing the schizophrenic disorders and the affective disorders. The trend in the California findings may well reflect increasing familiarity with these criteria. A category of schizoaffective disorder remains, without diagnostic criteria, for those instances in which a clinician is unable to make the differential diagnosis with any degree of certainty; it is not, however, as was formerly the case, included among the schizophrenic disorders but under a new category of "psychotic disorders not elsewhere classified." Such instances emphasize the need for careful diagnostic evaluation as an ongoing process.

In those instances in which the differentiation between a schizophrenic illness and an affective illness featuring manic symptoms is not clear, it is appropriate to institute a trial of lithium carbonate treatment. Such is particularly the case when response to neuroleptics is not satisfactory. The duration of such a trial, barring the development of adverse reactions, should be at least a month at adequate serum concentrations. Research

indicates that lithium is as effective in manic patients with "schizophrenic symptoms" as in those without.

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Ergot Alkaloids and Dementia

ALTHOUGH CLINICIANS have remained sceptical about the use of dihydroergotamine mesylate in treating senile dementia, it remains the only drug approved by the Food and Drug Administration (FDA) for use in "selected symptoms in elderly patients." Recent research findings may lead the way to more effective clinical use of this medication.

Historical review of studies of dihydroergotamine mesylate shows a general tendency for medication dosage to increase, starting with 1.5 mg per day in the early 1950s, to doses of 6, 9 and 12 mg a day at present. The dosage usually prescribed in the United States is 3 mg a day, whereas in Europe 4.5 mg a day is prescribed. In general, those studies done at higher doses report superior efficacy for the high-dose regimen. Of particular interest is a recent direct comparison of 3 mg versus 6 mg a day in more than 500 patients with cerebrovascular disease that found clear superiority for the higher dose.

Such studies improve our knowledge of dosage for dihydroergotamine mesylate but do little to improve our understanding of the rationale for its use. Proposed effects have shifted from improvement of cerebral circulation to effects on cerebral glucose metabolism to, most recently, neurotransmitter effects. Examining the recent comparison of 3 mg versus 6 mg leads to the question of why a drug with supposed effects on neurotransmitters has positive effects in a disease where the cause is structural—that is, cerebrovascular accident—or in other degenerative diseases of the brain. The behavioral rating subscales with greatest improvements were heavy-headedness, loss of concentration and loss of vigor. These results suggest that the drug probably has a positive effect on arousal and attention. Thus it may be that even with structural damage some improvement may be attained in clinical status by increasing aspects of the alertness-arousal-attention complex that may be mediated through other neural systems not injured by the initial attack.

The use of drug concentration determinations and biochemical tests to predict drug response is a fruitful area of research. Much has been written in the general psychopharmacologic literature about the use of metabolites of biogenic amines such as 3-methoxy-4-hydroxyphenylglycol (MHPG) to predict response to antidepressant medications. It has been well documented that major changes occur in biogenic amines with normal aging and also with neuropsychiatric diseases such as dementia, commonly found in the elderly. To date there has been only one preliminary study—by Samorajski and associates—correlating changes in serum prolactin with symptomatic improvement with dihydroergotamine mesylate treatment. This study examined the hypothesis that this ergoloid mesylate's therapeutic effect is related to its dopamine-agonist effects and that serum levels of prolactin fall with increasing agonist activity. Many other biochemical markers remain unexamined as predictors of psychopharmacologic treatments in the elderly with depression and dementia.

In conclusion, encouraging results indicate that doses higher than the FDA-approved 3 mg a day are potentially more beneficial. Further work will need to be done to document these dosage effects on populations in the United States and to further explore potential biochemical predictors of drug response and the benefit of combined therapy.

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Recent Developments in the Diagnosis of Childhood Depression

DEPRESSION IN CHILDREN has long been an area ignored by researchers. This has changed significantly in the past ten years as recent biologic and clinical advances in the study of adult depression have been duplicated in studies of childhood depression.

Several researchers have been working to obtain a consistent set of diagnostic criteria for childhood depression. The *Diagnostic and Statistical Manual of Mental Disorders, 3rd Ed* in 1980 stated that a child must either show a dysphoric mood or a pervasive loss of interest in almost all usual activities, in addition to at least four of the following eight symptoms: (1) change in appetite, (2) sleep difficulty, (3) psychomotor agitation or retardation, (4) loss of pleasure in usual activities, (5) loss of energy, (6) feelings of self-reproach or guilt, (7) complaints or evidence of diminished ability to concentrate and (8) recurrent thoughts of suicide or death. The duration of these symptoms must be longer than two weeks. It has been emphasized that though these criteria offer the advan-

tage of uniform applicability by researchers, they are the criteria for adult depression. Empirical research is necessary to determine how these criteria might vary with age and development.

Some researchers emphasize the difficulties involved in defining depression as a clinical phenomenon, the diagnosis of which can be based on the observation of a group of symptoms or an inference regarding some presumed underlying process. Nonetheless, consistent criteria, even with imperfections, are a considerable advantage to clinicians and researchers.

Biologic research is helping to refine criteria as it defines different subgroups of childhood depression. In one study of 18 dysphoric children aged 6 to 12 years, using the dexamethasone-suppression test, nine children were found to meet diagnostic criteria for a major depressive disorder, and eight of the nine met the diagnostic criteria for endogenous depression. Five of the nine depressed children had abnormal dexamethasone suppression, failing to have suppressed 4 PM cortisol concentrations the day after an 11-PM dose (0.5 mg) of dexamethasone. The results parallel the research completed in adults who have endogenous depression, suggesting that this illness is not rare in childhood and that it is clinically and neuroendocrinologically similar to the adult disorder. This test may have considerable clinical applicability. It is frequently used in adults with depressive symptomatology, and similar use can be anticipated for children.

A variety of neuroendocrine studies have been completed that validate the existence of childhood depression and confirm its similarity to adult depression. Some of these studies are linked directly to treatment, such as a study of imipramine response in children. Response to the antidepressant is clearly linked to the plasma concentration of the drug. Steady-state plasma concentrations of more than 150 ng per ml are associated with clinical response, and optimal responses were obtained at plasma concentrations above 200 ng per ml. Dose does not necessarily predict plasma concentration, so levels have to be monitored carefully, as with adults. Researchers have studied plasma levels of growth hormone at 15-minute intervals after the injection of insulin (which induces hypoglycemia), comparing the growth hormone levels of children meeting the research diagnostic criteria for endogenous depression, nonendogenous depression and a group with neurotic emotional disorder. Of the endogenous group, 90 percent were reported to have a peak growth hormone secretion in the first hour of less than 4.0 ng per ml. Virtually 100 percent of the neurotic group had levels above 4 ng per ml. A small group (10 percent to 15 percent) of children who have depression have an increased secretion of cortisol in a 24-hour period. Another study has found that the older a child, the more likely he or she will have this pattern.

These findings suggest a similarity to major affective disorders in adults but also imply age-related biologic effects. These findings further support the use of diagnostic criteria and suggest that there might be developmental effects. This is an area that will continue to be the subject of considerable investigation.

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Hysteria, Behavior and Physical Symptoms

THE TERM HYSTERIA has previously been used as a label for abnormal preoccupation with physical functions and complaints, conversion symptoms, amnesia and personality disorders. However, the current definitions published by the American Psychiatric Association in the *Diagnostic and Statistical Manual of Mental Disorders, 3rd Ed* have reorganized this broad spectrum of symptoms into more cohesive categories and thus should be reviewed by practitioners.

These newer definitions basically relabel and more clearly delineate previously recognized aspects of the diagnoses of hysteria. The one exception is hypochondriasis, which, as before, is an independent diagnosis characterized by an unrealistic interpretation of physical signs or sensations, often leading to preoccupation with the fear or belief in an actual serious physical disease.

Examples of the relabeling process can be seen in both the conversion disorder, which continues in the new diagnostic standards without the previous modifier "hysterical," and in the somatization disorder, previously described as Briquet's syndrome. The actual diagnostic criteria of both remain relatively unchanged. A conversion disorder is characterized by a loss or alteration in physical functioning, suggesting a physical disorder, but in reality is an expression of psychologic problems. In persons who have conversion disorders, difficulties usually develop in the voluntary nervous system or senses, frequently based on a precipitating event. Secondary gains are also common observations, that is, a person unable to obtain support from family and friends begins receiving reinforcement because of his or her "illness." Somatization disorders, as described in the *Diagnostic and Statistical Manual of Mental Disorders, 3rd Ed,* emphasize current, multiple somatic symptoms of years' duration, leading to frequent medical consultations that never result in adequate physical explanation of the symptoms.

An example of reorganization and updated diagnostic

criteria is evidenced by the disorder previously labeled hysterical personality and now incorporated in the current definition of histrionic personality. Persons suffering from hysterical or histrionic personality disorders show features of dramatic, intensely expressed behavior, emotional lability, exhibitionism, craving for activity and excitement, sexual problems, dependency, vanity and superficial manipulative interpersonal relations. The disorder often presents clinically in the form of verifiable physical symptoms that develop as a consequence of injury, illness or aging. However, patterns frequently emerge involving excessive complaints of the intensity of the disability, as well as dependent relationships (based on financial or emotional rewards) encouraging an unconscious motivation to continue the disability. Often drug or alcohol abuse is an associated symptom.

In the past, under the heading "hysterical personality," these symptoms were almost exclusively diagnosed in women and, indeed, were considered to be a distortion of the "usual" feminine characteristics. Recent clinical observation, however, incorporated into the new criteria for histrionic personality, has concluded the disorder exists in men as well as women and may be manifested by either effeminate passive qualities often seen in homosexual men, or in the newly recognized group of "macho" men, who show the same basic difficulties of dramatic, reactive, expressive, exhibitionistic, aggressive and manipulative behavior. Because this latter group often shows these behaviors with exaggerated stereotypes of masculinity (for example, dress, tattoos, fights, verbal abusiveness and motorcycles or automobiles), the critical characteristic is now considered a distortion of gender behavior with an exaggeration of *either* masculine or feminine characteristics.

The treatment of choice for the various diagnoses continues to be early psychotherapeutic intervention and a return to normal activities, though medications may be helpful for short-term or focal use in relieving symptoms of anxiety or depression. JOE P. TUPIN, MD

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The Newer Antidepressants

SEVERAL NEW ANTIDEPRESSANTS (maprotiline hydrochloride, trazodone hydrochloride, trimipramine maleate and amoxapine) have been marketed in the United States during the past few years. An additional 25 drugs are either currently marketed outside the United States as antidepressants or are in various stages of testing.

Claims of rapid onset of action for some of the newer antidepressants may be true for some patients, but to date none of the newer agents have consistently shown shorter response times than their older counterparts. Some of the new agents may be safer in overdose attempts, but unfortunately adequate assessment of a safety profile of a new antidepressant must await the evaluation of overdosing by many different persons.

It is not clear whether the newer antidepressants have distinctively fewer side effects than some of the older agents. However, particular side effects—for example, anticholinergic—may be lessened with some of the new antidepressants. A complete profile of the side effects for a particular drug (for example, tardive dyskinesia from long-term use of major tranquilizers) may take several years to emerge.

Several studies suggest that for a particular patient one antidepressant may be substantially more effective than another. The newer antidepressants may conceivably afford selected patients therapeutic benefits not available with older agents.

Following are some of the claimed advantages and possible disadvantages of the newly marketed antidepressants. Maprotiline possibly has a more rapid onset, lower cardiovascular toxicity and lower anticholinergic side effects, but also there is the increased possibility of skin rashes; trazodone possibly has a more rapid onset, lower cardiovascular toxicity and lower anticholinergic side effects, but also an increase in drowsiness; trimipramine has actions similar to older tricyclics, and amoxapine possibly has a more rapid onset but also some neuroleptic activity. MICHAEL J. GARVEY, MD

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Underdiagnosis of Physical Causes of Psychiatric Symptoms

PSYCHIATRIC SYNDROMES resembling depression, anxiety, mania and even schizophrenia often result from undiagnosed organic conditions. One study of more than 2,000 psychiatric clinic patients reported major medical illness in 43 percent of the sample. Almost half of these illnesses had not been diagnosed by the referral source (nonpsychiatric physicians had failed to diagnose 32 percent of these major medical illnesses, psychiatrists 48 percent and social agencies 83 percent). In almost 8 percent of cases, the medical illness was the cause of the patient's psychiatric signs and symptoms. Other studies have produced similar findings. Despite previous medical examinations, about 5 percent of psychiatric inpatients suffer from undiagnosed medical diseases causing their psychiatric disorders. In all likelihood organic causes also underlie a portion of the psychiatric symptomatology that goes unrecognized in medical inpatient and outpatient practices.

Of previously unrecognized organic illnesses, 90

percent can be diagnosed by a test battery that includes a careful history, physical examination (including a detailed neurologic examination) and mental status examination, plus laboratory studies that include a biochemical panel, a urine analysis, a complete blood count, an electrocardiogram and a sleep-deprived electroencephalogram (positive in 9 percent in one series). Diagnostic accuracy can also be increased by looking for organic causes for psychiatric symptoms in patients who have one or more of the following characteristics: age greater than 60 or initial onset of symptoms after age 40, signs of cognitive impairment, onset of symptoms in the absence of environmental stress, use of prescribed or over-the-counter drugs or exposure to industrial toxins. Finally, organic disease must be considered despite a patient's vague or dramatic physical symptoms, or a past history of hypochondriasis or "hysteria."

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Editorials

To the Young Doctors Who Are Just Now Starting Practice

YOU ARE ABOUT to enter a challenging, stimulating and fascinating career. Medical science has advanced far. Medical practice affects and is affected by events in the technologic, social, economic and political environment in new and as yet poorly understood ways. Both the science of medicine and the environments of practice are changing continuously and you will always be pressed to keep pace. But patients—the persons whose illnesses, health and quality of life are your professional concern—do not change all that much, nor does the humanity that populates the environment within which you will practice.

Your training, especially if American, places you among the best trained doctors scientifically that the world has ever known. Your training in what we call the art, that is linking your scientific knowledge and skills to caring for the needs of a patient as a whole person, may have left something to be desired, as may your training in the social, economic, legal and political aspects of medical practice and of the health care system within which you will work.

Paradoxically it is the progress in medical science in which you are so well trained that has created many of the as yet unsolved problems in the health care environment. Very briefly, this progress has brought about significant specialization and subspecialization within our profession and an unprecedented proliferation of allied health professionals who now seek to advance their professional status and expand their scope of practice. As new knowledge and new technology have come into being, diagnosis and treatment have become more effective, life expectancy has been substantially extended and more people are requiring more of your care. As the number of health professionals has increased, as more sophisticated and effective diagnosis and treatment have become more widely available and used, and as more people need and use more care, the expense has risen in apparently uncontrollable fashion. In one way or another costs now will dominate your practice. So you must be careful that you always try to do what is best for your patients in what will be a very cost-sensitive health care environment.

Society is confused about what to do about health care and its rising cost. You must remember it is society that decides the scope of medical practice and it is society that decides what it will pay for health care. Society has said it wants more health care for more people and equal access for all to high quality care, but is now balking at the expense. Many attempts have been made to control costs through laws and government regulations but these have not worked, perhaps because our legal system is ill-adapted to regulate or control a system that changes as rapidly and continuously as does health care. Right now society is trying to view health care more as a business or many businesses competing with one another. It is attempting to introduce competition and business practices into the system in the probably forlorn hope that this will lessen costs. This approach threatens the quality of patient care and of course makes a travesty of equal access for all to quality care. There will be agreements or contracts to provide care that will tend to go to the lowest bidder. As is the case in any business or industry, patients or the public will get the amount and quality of care they are willing to pay for. So as you start your practice now it will be in a volatile economic environment whether you choose to be solo, in a private practice group, in a health maintenance organization (HMO), in an independent practice association (IPA), a hospital-based physician, in the employ of one of the rapidly emerging corporate organizations or some other arrangement. Regardless, it is important that you never forget that your primary obligation is the historic responsibility of doctor to patient. This always must come ahead of any business or corporate responsibilities.

Medicine is a grand profession. It is a fascinating amalgam of science, caring and human compassion, and now with yet new human dimensions, as technology poses ethical problems, and as new and growing social, economic and political interdependencies begin to demand new knowledge and new skills of our profession and those who practice it. It seems certain that the expertise of medicine will find new means of expression as humanity struggles for health and quality of life in this closed biosphere called planet Earth, with its intrinsically complex and interdependent networks of technologic, social, economic and political systems which impinge in one way or another upon human illness, health and quality of life. There will be many new challenges and opportunities to develop new knowledge, skills and expertise to benefit patients and improve the health of all the people.

You will see and be part of many changes. You and our profession should remain steadfast in our basic purpose: to provide the best care and treatment for patients. Changing science and changing practice environments will challenge you to maintain and enhance your professional competence and your accountability for your practice performance. The social, economic and political whirlwind in which you are starting your practice will pose many foreseeable and some not so foreseeable problems. Fortunately your skills in problem solving are highly developed and can now be adapted for use far beyond the basic diagnosis and treatment of illness for which you were trained. Take care of your own health. You owe this to your-

selves, your families, your patients and to society which gives you your license to practice. You are entering practice at a time of unprecedented challenge and excitement. It should be both fun and satisfying for you to face and meet these many challenges. I wouldn't mind being one of you!

—MSMW

Seizures From Theophylline Use

IN A RECENT two-year study of theophylline toxicity,[1] 17 percent of 3,112 serum theophylline concentrations were greater than 20 μg per ml, the upper limit of the usual therapeutic range. Of 87 patients with serum theophylline concentrations higher than 20 μg per ml, almost all had one or more symptoms or signs of toxicity, including tachycardia, tremor, nervousness, irritability, nausea, vomiting, diarrhea, headache and seizures. Of 19 patients who had values of more than 40 μg per ml, four had seizures. None of the patients with values below 40 μg per ml had seizures. Seizures from theophylline can result in status epilepticus and can have a fatal outcome. In one series[2] four of eight patients with seizures due to theophylline use died. Seizures have been reported with intravenously given aminophylline, orally given theophylline[3] and aminophylline given by suppositories.[4] Suicide attempts have been made by ingesting an overdose of theophylline. Of nine such suicide attempts described in one report, three of the nine patients had seizures and those three died.[5] The six who did not have seizures survived.

Seizures from theophylline use usually occur with serum theophylline concentrations above 35 μg per ml.[2] Other side effects clearly occur with concentrations within the therapeutic range of 10 to 20 μg per ml.[6] Several individual cases have now been reported in which patients had seizures due to theophylline use, with theophylline concentrations of less than 35 μg per ml.[2,7] Nakada and colleagues in this issue of the journal add three more patients to this group; their three patients had seizures likely from theophylline use with theophylline values of 17, 20.5 and 24 μg per ml at the time of the seizures. Results of an autopsy done on two of the patients showed no structural lesion in the brain to explain the seizures. One possible explanation for seizures occurring at low theophylline concentrations is decreased binding of theophylline to plasma proteins, making more free drug available for diffusion into tissues.[8] Nakada and co-workers did not measure the amount of theophylline bound to protein, though all three of their patients had low serum albumin levels.

Treatment of seizures from theophylline toxicity is difficult, making prevention of paramount importance. The seizures are refractory to anticonvulsive medication. Theophylline therapy should be stopped immediately and the theophylline concentration should be decreased as soon as possible. Resin and charcoal hemoperfusion has been reported to reduce theophylline concentration, but a recent review of renal dialysis for theophylline toxicity points out that even with rapid reduction of the serum theophylline value the outcome has not always been favorable.[9] For attempted suicide with theophylline overdose, vomiting should be induced, then activated charcoal and cathartics given.[9]

Prevention of theophylline toxicity requires some knowledge of pharmacokinetics of theophylline. The half-life varies in asthmatic adults who are otherwise healthy from 2.9 to 12 hours.[7] Similar variation occurs in children. Thus, one dosage schedule is not applicable to all patients. Serum theophylline values should be used to guide therapy. Guidelines for theophylline therapy have been published,[7,9,10] and a patient's past experience with theophylline should be considered.

Diseases that prolong the theophylline half-life and thus require a decreased dose include congestive heart failure, liver disease, influenza and possibly other respiratory and febrile illnesses.[7] A growing number of drugs that are being reported to delay theophylline metabolism also require a reduction in the dose. Troleandomycin,[11] erythromycin[12] and cimetidine[13] are well-documented examples. Furosemide,[14] thiabendazole,[15] allopurinol at a dose of 600 mg per day but not at 300 mg per day,[16] propranolol but not metoprolol,[17] hydrocortisone[18] and influenza immunization[19] have all been reported to delay theophylline metabolism and thus could cause toxicity in patients on stable theophylline regimens.

Seizures are an uncommon but serious complication of theophylline therapy. Most of these seizures result from toxic theophylline serum concentrations and can be prevented by application of pharmacokinetic knowledge of theophylline use and by monitoring therapy with measurement of serum theophylline values.

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Case Reports

Low-Dose Propranolol Therapy for Aborting Migraine

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ERGOTAMINE GIVEN ORALLY has been the mainstay therapy for aborting acute migraine headaches despite questionable efficacy,[1,2] significant side effects[3] and toxicity.[4] Propranolol hydrochloride administration, meanwhile, has been found to be effective and safe in the prophylactic treatment of migraine.[5,6] Little attention has been given to propranolol as an abortive agent, however; in 1978 Tokola and Hokkanen[7] reported in a letter that an uncontrolled series of patients with acute episodes of migraine was successfully treated with administration of 40 to 120 mg of propranolol. Headache pain resolved or lessened in 53 percent of their patients in two hours without any serious adverse reactions. The following case reports reemphasize the abortive value of giving low doses of propranolol to some migraine patients.

Reports of Cases

CASE 1. A 33-year-old housewife with a 13-year history of occasional classic and frequent common migraine headaches was placed on a regimen of 10 mg of propranolol taken four times a day for frequent severe, unilateral, throbbing headaches associated with nausea and lasting 48 to 72 hours. A month after starting propranolol therapy, the patient reported she had discovered that she could abort headaches within 30 minutes by taking 10 mg of propranolol at the start of one. She had discontinued daily propranolol use in favor of abortive use, which, after 18 months of therapy, continues to control her headaches.

CASE 2. A 48-year-old male business executive with an 18-year history of occasional severe, unilateral, frontal, throbbing headaches associated with nausea and vomiting was started on a regimen of propranolol, 10 mg four times a day, for a one-week history of daily headaches of the same pattern. At his next visit, the patient reported that he had found that a single 10-mg tablet of propranolol taken at the onset of a headache totally alleviated the attack in 15 to 30 minutes. He had discontinued daily propranolol use. Abortive propranolol therapy is still effective after 36 months of use.

CASE 3. A 53-year-old housewife with a "lifelong" history of headaches often associated with nausea and a pressure-band sensation around her head, and often lasting three to four days, discovered that one to four 10-mg propranolol tablets taken at the onset of a headache would shorten the duration of the headache and reduce its intensity within 60 minutes. This effect was augmented by taking aspirin simultaneously with the propranolol. A trial of propranolol prophylaxis was discontinued because of severe fatigue and weakness. Abortive propranolol therapy was effective for eight months before being discontinued on abatement of her headaches.

CASE 4. A 50-year-old woman, a secretary, with a 27-year history of frequent episodes of throbbing bilateral maxillary pain radiating to the left temple and associated with nausea and vomiting, was started on propranolol prophylaxis, 10 mg taken three times a day. She returned after finding that administration of 30 to 40 mg of propranolol, if taken at the onset of the pain, aborted or reduced the intensity and duration of her headache within 30 to 60 minutes. She subsequently became depressed on propranolol prophylaxis of taking 40 mg four times a day and currently continues to use propranolol effectively in an abortive fashion, 40 months after first noting the effect.

CASE 5. A 29-year-old woman, who is a telephone company representative and the daughter of the patient in case 4, had a 16-year history of pain very similar to her mother's. She was started on propranolol prophylaxis, 40 mg taken three times a day. Within a month the patient reported that her headaches were effectively aborted in 15 to 30 minutes by taking 40 mg of propranolol and two aspirin tablets at the beginning of a headache. Propranolol alone was less effective, aspirin alone was ineffective. The patient discontinued prophylactic use of propranolol in favor of abortive use, which continues to be effective after 36 months of use.

CASE 6. A 35-year-old male physician with a 20-year history of frequent throbbing, unilateral, frontal headaches associated with nausea was started on prophylactic propranolol therapy, taking 20 mg three times a day. Within two weeks he reported that his headaches were relieved or greatly attenuated in 30 minutes by taking 20 mg of propranolol at their onset. He discontinued daily prophylaxis in favor of abortive use of propranolol, which he continues to find effective after 15 months of use.

Discussion

In these six cases propranolol therapy was apparently effective in aborting acute migraine headaches, mostly in patients who had common migraine. Because pro-

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pranolol is not approved for abortive use,[8] none of these patients was instructed to take the medication in this fashion; all discovered spontaneously the abortive effect, which occurred with 10 to 40 mg taken orally. The action of the drug usually became manifest at about 30 minutes and was not accompanied by untoward effects. The effective dose and the time needed for relief of symptoms were both less in this series than in that of Tokola and Hokkanen.[7] Propranolol thus appears to be useful and safe as an abortive agent in some migraine patients. The reported combined effectiveness of aspirin and propranolol in two cases implies possible synergism, which needs further investigation.

The mechanism of action of propranolol in migraine is not known.[6] Propranolol is rapidly absorbed after oral administration, has a peak effect at 1 to 1½ hours and a half-life of three to six hours.[8] It is contraindicated in bronchospastic lung disorders, congestive heart failure, cardiac conduction defects and in patients receiving hypoglycemic therapy or monoamine oxidase inhibitors.

Because the effect of placebo in acute migraine appears to be great,[1] controlled trials comparing propranolol with placebo and other abortive agents are indicated to determine the abortive value of propranolol therapy; no such trials have been reported in the literature to date. Other issues to examine include the optimal dose of propranolol, the factors involved in selecting patients best suited for abortive therapy with propranolol and the effectiveness of propranolol use alone versus propranolol with aspirin. If propranolol is effective as an abortive agent, it may offer many advantages over oral ergotamine, which may be no more effective than placebo[1,2] and with chronic use may be associated with increasing headache, nausea, peripheral vascular insufficiency and neuropathy.[4,9] Propranolol could be the aborting agent of choice for migraine patients who have hypertension, coronary artery disease, thyrotoxicosis or peripheral vascular disease. In addition, some patients who are successfully managed on propranolol prophylaxis may be controlled on abortive therapy alone, thus reducing the cost and potential side effects of daily prophylactic use. Propranolol has received curiously little attention as an agent for aborting acute migraine; it is time to define its utility in this role.

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Successful Medical Management of Bilateral Ureteral Obstruction Due to Acute Uric Acid Nephropathy

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URINARY TRACT OBSTRUCTION can present in several guises depending on the acuteness of onset, degree of obstruction and location. Acute unilateral obstruction as with stones occurs with hematuria and severe flank pain resulting from a sudden rise in renal pelvic pressures to levels exceeding 50 mm of mercury.[1] Partial bilateral obstruction may give no signs or symptoms referable to the genitourinary tract, yet a patient may have advanced renal failure. Anuria with or without pain occurs with complete bilateral obstruction, depending on the time course. Management of all of these forms of obstruction is directed towards the cause, with a surgical procedure often done in many clinical situations. Whereas nonsurgical treatment is possible for small stones (usually less than 5 mm), some blood clots or sloughed papillae, a patient with flank pain, azotemia and ureteral obstruction is usually treated by a procedure to reduce pressure in the renal pelvis.

We describe a case of acute uric acid nephropathy that mimicked sudden ureteral obstruction and had elements of both intrarenal and extrarenal obstruction. Despite symptoms and changes found on pyelography study (with contrast dye given intravenously) that were compatible with complete bilateral obstruction, the patient was treated successfully by medical means.

Report of a Case

A 62-year-old man who had anuria was transferred from another hospital in August 1980. His history was as follows: He was well until 1976 when easy bruising and leukocytosis developed and a diagnosis of chronic lymphocytic leukemia was subsequently made. The patient was treated intermittently with administration of chlorambucil. In January 1980 the peripheral leukocyte count was found to be 5,000 per μl, the hematocrit 30 percent and the platelet count 20,000 per μl. Despite discontinuation of chemotherapy, the leukocyte and platelet counts remained depressed. An enlarged spleen was palpated, findings on a liver-spleen scan in July confirmed splenomegaly and a splenectomy was advised. He was taking hydrochlorothiazide, 50 mg, by

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Figure 1.—Abdominal plain film taken 12 hours after intravenous injection of contrast dye and showing bilateral ureteral and renal pelvic dilatation indicating obstruction.

mouth daily for mild peripheral edema. A ten-day course of external-beam radiation treatments to the splenic region was begun in late July. After the patient had received his ninth radiation treatment, progressive right lower back pain developed, which was worse with movement or local pressure. He was admitted to a nearby hospital the next day because of bilateral flank pain. The patient was afebrile and normotensive, but he had ecchymoses and a guaiac-positive stool test. The spleen was palpable but smaller. The leukocyte count was 3,800 per μl, the hematocrit 15.1 percent and the platelet count 3,000 per μl. Urine analysis showed a specific gravity of 1.011; on microscopic examination there were 30 to 50 erythrocytes, 0 to 2 leukocytes and many uric acid crystals per high-power field. After initially urinating, the patient produced no urine for 24 hours. Pyelography (intravenous) was done, resulting in no visualization of the urinary tract. He was transferred to the Naval Regional Medical Center, San Diego.

There was no history of renal parenchymal disease, kidney stones, urinary tract infection, diabetes or hypertension. The patient said he had no nausea but was observed to be retching intermittently. He noted a 14-kg (30-lb) weight loss during the preceding six months, with associated night sweats but without fever. His temperature was 36°C (97°F) orally, pulse rate 78 per minute and regular, blood pressure 120/80 mm of mercury and respirations 16. The neck veins were visible at 30 degrees and collapsed on inspiration. A 2/6 systolic murmur was heard at the left sternal border. Soft bibasilar rales were audible. The abdomen was distended and hypoactive bowel sounds were heard. He had hepatosplenomegaly, trace pretibial edema and a Foley catheter in place and multiple skin petechiae and ecchymoses were seen.

Laboratory studies on admission gave the following values: serum sodium 129, chloride 101, potassium 5.0 and bicarbonate 17 mEq per liter (normal 21 to 28); serum calcium 7.5 (normal 9.2 to 11.0), phosphorus 9.4 (normal 2.3 to 4.7) and uric acid 20.5 mg per dl (normal 4.0 to 8.5). The hematocrit was 22.5 percent, leukocyte count 4,500 per μl and platelets 18,000 per μl. A prothrombin time was 11 seconds (control of 12) and partial thromboplastin time 32 seconds (control 31 seconds). The blood urea nitrogen level was 75 mg per dl (normal 8 to 23) and the serum creatinine level 5 mg per dl (normal 0.6 to 1.2). Despite irrigation of the Foley catheter, no urine was available for analysis.

Chest x-ray films showed pulmonary venous hypertension. An abdominal series showed pronounced obstructive changes in both ureters (Figure 1). A presumptive diagnosis of acute urate nephropathy was made and therapy instituted with intravenous administration of allopurinol and hemodialysis. An initial six-hour hemodialysis reduced the serum uric acid concentration to 10.6 mg per dl. Six hours later the patient began to have urine output and the low back pain resolved. He received dialysis a second time for six hours on the second hospital day. No further hemodialysis was necessary. He continued to have diuresis and by the fourth hospital day the following laboratory values were obtained: serum creatinine 1.2, blood urea nitrogen 18, calcium 7.5, phosphorus 2.4 and uric acid 5.3 mg per dl. Medication at that time included allopurinol, 100 mg taken by mouth twice a day. By the time of discharge, the creatinine clearance was 55 ml a minute (normal 107 to 139) with a normal 24-hour protein excretion. Bone marrow examination showed the pancytopenia to be due to lymphocytic infiltration. Before discharge the patient was treated with administration of vincristine sulfate, prednisone and cyclophosphamide and had no recurrence of hyperuricemia.

Discussion

The patient had acute hyperuricemic nephropathy precipitated by splenic irradiation with elements of both extrarenal and intrarenal obstruction. This nephropathy, first described by Bedrna and Polcak in 1929,[2] results from the hyperuricemia caused by breakdown of purine nucleic acids. Although acute uric acid nephropathy may be the presenting feature of neoplastic disease,[3] it more commonly occurs after the initiation of therapy in patients with hematologic malignancy.[4] A urinary uric acid-to-creatinine ratio exceeding 1.0 is a highly specific indicator[5]; we could not assess this, however, due to

anuria. Clinically, Kelton and others have emphasized that a serum uric acid of greater than 20 mg per dl is usually present with acute urate nephropathy.[4,5]

Under debate is the question of whether the pathophysiology of renal failure reflects parenchymal deposition or intratubular obstruction.[4,6] The presenting symptoms may shed some light on the issue. In early reports patients sought medical care because of colicky flank pain, hematuria and unilateral or bilateral obstruction found on intravenous pyelography.[7,8] In several of the reported cases, patients underwent maneuvers that removed sludge or stones (or both), for example, ureteral lavage and stone removal, or had bypass procedures such as nephrostomy or ureterostomy. Forced diuresis was initiated after the invasive procedures removed the obstruction. In a review of contemporary cases, Kjellstrand and co-workers[4] state that the presenting symptoms were more often those associated with renal failure such as nausea, fatigue and lethargy, with no patients describing symptoms referable to acute ureteral obstruction. These patients responded well to hydration and dialysis. In retrospect, there seems to be a definite change in the presentation of hyperuricemic nephropathy from a more acute obstructive one to a more insidious form. Whether this relates to awareness of the potential value of such prophylactic measures as hydration and allopurinol administration or to the chemotherapeutic modalities now used remains speculative. Because of the few chemotherapeutic agents formerly available, five of the ten patients reported on by Kritzler in 1958[7] received primary radiation therapy, versus 1 of 21 in Kjellstrand and colleagues' review.[4] The earlier investigations, moreover, included many cases of chronic leukemia, suggesting that the latter may be predisposed to an "obstructive" phenomenon.

The patient described here had the classic obstructive symptoms of back pain, costovertebral angle tenderness, hematuria and anuria. The abdominal plain film done 12 hours after pyelographic dye injection (Figure 1) showed obstruction of both ureters and the serum uric acid level was in the appropriate range for uric acid nephropathy. Uric acid crystals were prominent in the urine specimen obtained before transfer. Hyperphosphatemia is often associated with acute renal failure, especially with oliguria, and it may have contributed to the decline in glomerular filtration rate. Dye-induced renal failure was unlikely as a major cause because the intravenous pyelography study was done after the patient already had renal failure and oliguria. A diagnosis of acute uric nephropathy seems appropriate.

Despite meeting surgical criteria for a decompressive procedure (obstruction, pain, anuria and progressing azotemia), it was elected to treat the patient conservatively because of the high surgical risk present and the acknowledged success of medical therapy for nonobstructive acute urate nephropathy.[4,9] Fortunately, there is evidence that renal function will return even when the decompression of complete obstruction is not immediately done.[10] A six-hour hemodialysis procedure via femoral vein catheters reduced the serum uric acid level from 20 to 10.6 mg per dl. Without any surgical procedure, diuresis ensued and renal function returned. While the medical approach was successful, it should be added that in certain hands the prompt passage of ureteral catheters may likewise yield a good result, at least for the extrarenal element of uric acid obstruction. Such catheters can be irrigated with sodium bicarbonate solution.

Although acute ureteral obstruction is now an unusual occurrence in hyperuricemic renal failure, it should still be considered in the differential diagnosis of acute renal failure in a patient treated for hematologic malignancy. In view of the low risk to recovery of renal function of temporizing with dialysis and adequate hydration and the minimal risk of one-time hemodialysis via femoral vein, we advocate dialysis as an initial medical approach to treating acute uric acid nephropathy, even in the presence of signs, symptoms and radiographic evidence of significant extrarenal obstruction.

Summary

The care of patients with ureteral obstruction often involves a surgical procedure or retrograde instrumentation for treatment of anuria, infection or secondary decline in renal function. We report the case of a 62-year-old man with bilateral ureteral and renal obstruction due to acute uric acid nephropathy following splenic irradiation in the course of treating chronic leukemia. He was admitted with flank pain and fever, and after admission anuria with progressing azotemia developed. Despite indications for a decompressive procedure, he was treated with hemodialysis and achieved an abrupt relief of urinary obstruction within hours. Review of the literature showed a disparity in presentation between early cases of acute uric acid nephropathy and more recent reviews. The recent cases were rarely precipitated by radiation therapy and had no obstructive symptoms. Our case shows the older, infrequently reported obstructive phenomenon that, despite surgical indications, may at the outset be approached medically.

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Vaccine-Related Poliomyelitis: Serum IgM and Cerebrospinal Fluid Antibodies

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ABBREVIATIONS USED IN TEXT

IgG = immunoglobulin G
IgM = immunoglobulin M

THE INCIDENCE of poliomyelitis in the United States has fallen to fewer than 20 cases a year.[1-5] Most recent cases are caused by the vaccine strains of poliovirus, and almost two thirds occur in contacts as opposed to vaccine recipients. In contact cases the virus generally spreads by the oral-oral rather than the fecal-oral route, with an interval of 20 to 29 days from vaccine administration to paralytic disease. Typically, the diagnosis is based on the history and clinical presentation, an increasing serum titer of antipoliovirus antibody and isolation of vaccine-strain virus from the gastrointestinal tract. We report a contact case that was clinically typical for poliomyelitis. However, the laboratory diagnosis in this case was based on the findings of special studies: the presence of serum immunoglobulin M (IgM) antibodies to poliovirus and an increasing titer of antipoliovirus antibodies in the cerebrospinal fluid.

Report of a Case

The patient was a 43-year-old contractor who had never been immunized with poliovirus. His 3-month-old grandchild had recently received the oral trivalent vaccine. About five days after this immunization, the patient was holding the child above his head and some saliva passed from the infant into his mouth. He washed his face and rinsed his mouth with water. About five days after this contact, the patient began to have a mild fever, sore throat and an overall sluggish feeling. These symptoms persisted but in diminishing severity. About 19 days after contact he felt much worse, had a fever to 39°C (102°F), posterior headaches, low back pain and an ache in his buttocks and legs. Two days later he awoke in the morning with weakness in both lower extremities. This weakness progressed in 12 hours to complete paraplegia. There were no sensory symptoms.

The patient was admitted 23 days after contact to the University of California, Davis, Medical Center. His temperature was mildly elevated at 37.4°C (99.4°F). The general physical examination showed no other pertinent abnormality. On neurologic examination his sensorium was clear, and there was no sign of a thought or language disorder. Findings on cranial nerve examination were also normal. On motor examination the lower extremities were found to be flaccid, areflexic and paralyzed. In the upper extremities, strength and coordination were normal and deep tendon reflexes were graded as 2+. Bladder function was intact after some initial difficulty with voiding. Sensory examination showed no abnormality in the appreciation of soft touch, pin, cold, vibration or joint position sense.

The patient's fever abated on the third hospital day but his neurologic state remained unchanged except for the gradual development of wasting in his lower extremities. Spinal fluid examination showed a mononuclear pleocytosis of 537 cells and a protein level of 62 mg per dl on the first hospital day, 455 cells and a protein level of 49 mg per dl on the fourth hospital day and 41 cells and a protein level of 143 mg per dl on the 14th hospital day.

Electrodiagnostic tests were done 8 days, 11 days, 4.5 months and 8.5 months after onset of paralysis. Eight days after paralysis, motor and sensory nerve conduction studies in the legs showed normal velocities, distal latencies and evoked-potential amplitudes. The only electromyographic abnormalities were occasional positive sharp wave potentials in the lumbosacral spinal muscles and the absence of motor unit action potentials in the legs. Eleven days after paralysis, there was absent motor conduction but normal sensory conduction in the legs. Abundant positive, sharp wave and fibrillation potentials were present in leg and lumbosacral paraspinal muscles. Voluntary motor unit action potentials were still absent. At 4.5 months after paralysis, nerve conduction studies still showed absent motor but normal sensory conductions. A few low-amplitude (50 to 100 μV) long-duration (20 to 30 msec) polyphasic motor unit action potentials were noted in the right vastus medialis muscle. Otherwise, results of the electromyographic study were unchanged. The only additional finding 8.5 months after paralysis was a few large-amplitude (10 mV) prolonged duration (15 to 18 msec) motor unit action potentials in the right vastus medialis and iliopsoas muscles.

Despite an intensive rehabilitation program, the patient remains wheelchair-dependent and has had no significant functional recovery of motor power in his legs.

Laboratory Confirmation

Poliomyelitis was suspected on the basis of the clinical presentation. Laboratory confirmation proved to be difficult, however. Viral cultures of specimens of cerebrospinal fluid, stool and pharyngeal secretions were all negative. Neutralizing antibodies against all three poliovirus serotypes were present in the serum. As shown in Figure 1(A), the titers were high without significant fluctuations (1:512 to 1:2,048). This result

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indicates a prior infection at an unknown time. To establish the presence of a recent infection, serum was fractionated and assayed for IgM antibodies. Low titers (1:8) of IgM antipoliovirus antibodies were present 28 days after the presumed contact but no IgM antibodies were detected at 60 days (titer less than 1:4). This finding suggests that a recent infection had occurred, though it is not certain whether this infection was the patient's first contact with the virus or a reinfection.

There is a formal possibility that the neurologic disease was unrelated to the systemic poliovirus infection. Changes in cerebrospinal fluid antibody titers, however, strongly incriminate poliovirus in a central nervous system infection. Titers increased from 1:4 to 1:8 on the third day of paralysis to 1:32 on the sixth day and 1:64 to 1:128 on the 16th day of paralysis (Figure 1-B). The rise in titer in cerebrospinal fluid but not in serum suggests in situ central nervous system formation of antipoliovirus antibodies. A less likely explanation is that the changes in titer reflect a breakdown in the blood-cerebrospinal fluid barrier, with progressive leakage of serum immunoglobulin into the cerebrospinal fluid. This alternative seems unlikely because the antibody titers increased eightfold, whereas the total cerebrospinal fluid protein concentration remained unchanged between the third and sixth day of paralysis. Also, if a leaky barrier was the explanation, one would expect other viral antibodies present in serum to appear in the cerebrospinal fluid, and this result was not seen. For example, antibody to coxsackievirus B_2 could not be detected in cerebrospinal fluid (titer less than 1:4) despite a modest titer of 1:128 in serum. Unfortunately for this purpose, the patient had low serum antibody titers (1:8 to 1:32) to other common viruses that could serve as indicators of a blood-cerebrospinal fluid leak (for example, mumps, herpes simplex, rubella, measles). Independent evidence of immunoglobulin formation in the central nervous system comes from the immunoglobulin G (IgG)-albumin index (cerebrospinal fluid IgG:albumin divided by serum IgG:albumin). On the sixth day of paralysis, this index rose to 1.12 (normal less than 0.66). This abnormality occurs in central nervous system infections and demyelinating diseases.[8]

Discussion

The clinical features in this case are those seen in cases of poliomyelitis: an incubation period of 21 days, a biphasic course (minor illness followed by meningoencephalitis) and lower motor neuron involvement without sensory symptoms or signs. Electrodiagnostic findings confirm the clinical impression of severe anterior horn cell disease and argue against primary involvement of peripheral nerves as in postinfectious polyneuritis (the Guillain-Barré syndrome).[9] Preservation of normal sensory nerve conduction indicates the selectivity of the process. The eventual loss of motor conduction in the lower extremities indicates neuronal destruction and axonal degeneration. This finding of absent motor conduction carries a poor prognosis for functional recovery in poliomyelitis.[10]

The long incubation period in this case probably explains our difficulty in confirming the diagnosis by standard laboratory procedures. In most cases of poliomyelitis, virus cannot be isolated from the cerebrospinal fluid but may be identified in specimens from the

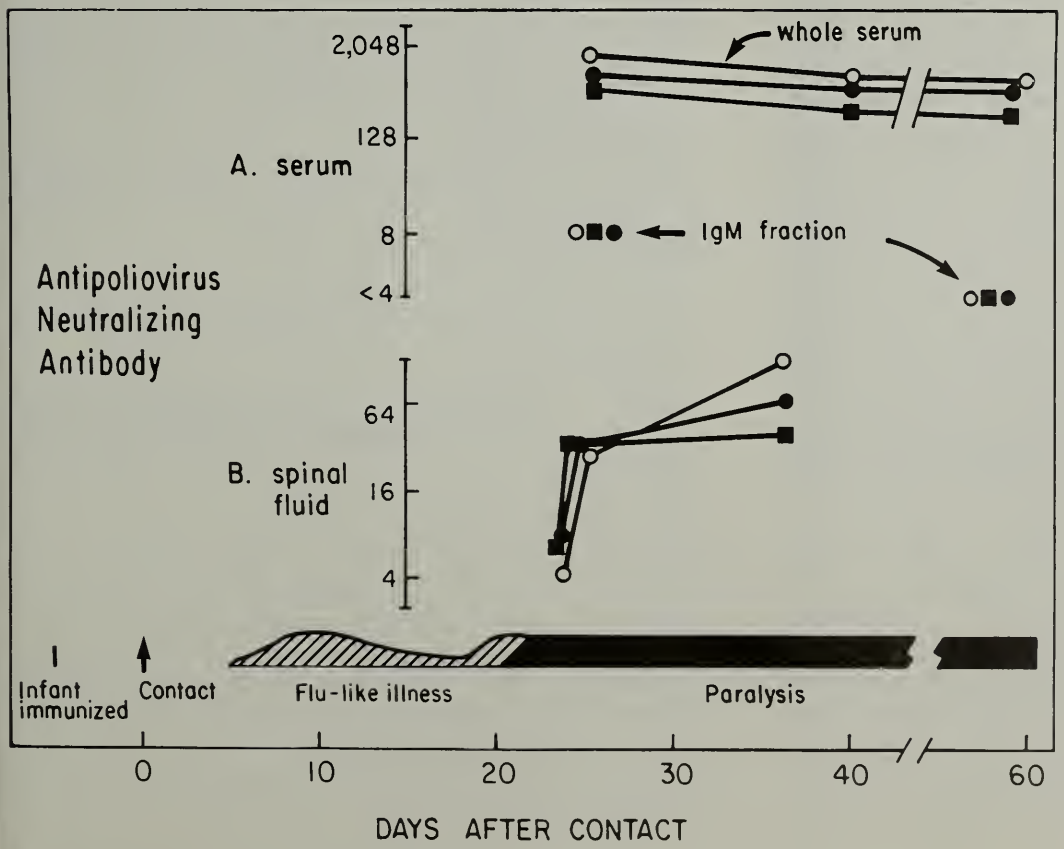

Figure 1.—Serum and cerebrospinal fluid antipoliovirus neutralizing antibody during the course of the disease (serotype: type 1 ●, type 2 ■, type 3 O). These tests were done under supervision of Dr Nathalie J. Schmidt at the Viral and Rickettsial Disease Laboratory, Department of Health Services, Berkeley, California. The neutralization titer is expressed as the reciprocal of the highest twofold dilution of serum or cerebrospinal fluid that neutralizes a test dose of virus containing 100 to 320 tissue culture infectious doses ($TCID_{50}$).[6] For IgM antibody determination, serum was fractionated by sucrose density gradient centrifugation.[7]

pharynx for up to three to four weeks after exposure and from the bowel for two to six weeks or longer after exposure.[2] The initial cultures from this patient were done on specimens obtained a little more than three weeks after contact, and it is possible that virus was cleared from these sites just before this time. Similarly, serum antibody titers had probably risen to a plateau just before the first specimen was drawn four weeks after contact. In contrast, cerebrospinal fluid was obtained early in the course of the central nervous system infection, allowing detection of an increase in titer from in situ formation of immunoglobulin.

All three poliovirus serotypes show serum IgM antibodies and a rise in cerebrospinal fluid antibodies. This unexpected result suggests an infection of all three serotypes. However, it has been shown that enterovirus infections can recall IgM antibodies to heterologous viruses; so it is possible that some of the IgM poliovirus antibodies occurred on this basis.[11] Similarly, there is a report of the development of poliovirus antibody in the cerebrospinal fluid during echovirus 6 infection.[12] The mechanism here is uncertain but may involve a blood-cerebrospinal fluid barrier leak. As noted in the previous section, a leak is an unlikely explanation in the present case. In summary, alternative explanations can be proposed for each of these laboratory test results. But, taken together with the consistent clinical and electrodiagnostic evidence, these tests provide support for the diagnosis of poliomyelitis. In suspected cases, it is advisable to do serum IgM and cerebrospinal fluid viral antibody titers in addition to the standard laboratory diagnostic tests for poliomyelitis.

Paralytic polio is more likely to occur in nonimmune adult contacts than in infants who receive the vaccine.[4] Both a viral and a host factor explain this increased risk. First, it is known that the attenuated virus used for immunization can become more virulent after passage in vaccinees.[1] With this in mind, it was recently suggested in a *Lancet* editorial that susceptible parents take the oral trivalent vaccine along with their infants.[13] A problem is the lack of protection of other potential contracts—such as the grandfather in the present case. Moreover, this procedure does not take into account the age-related host factor in poliovirus infection. Risk of contracting paralytic disease increases with the age of an infected patient.[14] It was in part for this reason that routine poliovirus immunization of adults was discontinued several years ago. Because type 3 poliovirus was widely known to account for most of these cases,[1] many persons chose to avoid the type 3 monovalent vaccine and are now susceptible to systemic infection with type 3 poliovirus. Unexpectedly, most of the recent contact cases have been due to type 2 and not type 3.[1,4,5] This possibly indicates a greater propensity for the attenuated type 2 virus to become more virulent after passage.

Vaccine-associated poliomyelitis could be avoided by widespread adoption of formalin-fixed vaccine, as Salk has suggested.[3] Experience with this vaccine in Finland and Sweden has shown excellent protection from paralytic disease, eradication of wild type virus and very few side effects.[15,16] The question remains whether the results would be as good in larger countries—such as the United States—that have less organized health care delivery. Most public health authorities would consider the small risk associated with the oral trivalent vaccine to be acceptable. The present case emphasizes that warnings of this risk should not be limited to parents but should include other nonimmune adults who have close contact with vaccinees.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgement before publication.

Medical Education and Family Medicine

TO THE EDITOR: I read with keen interest the editorial "Is It Time for a Fundamental Reexamination of Medical Education?" in the November issue.[1] Your perceptions regarding deficiencies in current medical educational practices are cogent, indeed. It seems timely for more attention to be paid to the wholeness of the person, the oneness of medical science and the emotional, economic, social and political impact of modern technology.

Your comments regarding the need to develop means for self-directed lifelong learning are also well taken. You may be interested to know that this approach is precisely the one being taken in family practice residency training programs across the country. The 7,204 residents in 387 residency programs in the United States are being taught the art of humanistic patient- and family-centered medicine along with the content and skills of the various disciplines vital to the broad range of needs of the American public.

With respect to lifelong learning, the American Board of Family Practice was the first in the nation to require recertification by written examination and office record review every six years.

We in family medicine have always known we were right to be training the "Renaissance physician." It is heartwarming, indeed, to see the Western states' most prestigious medical journal agree.

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REFERENCE

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Late Complications of Tricyclic Antidepressant Overdose

TO THE EDITOR: Callaham's November 1982 review[1] of criteria for monitoring and admitting patients who have ingested tricyclic antidepressants (TCA) provides a timely and useful discussion of the difficult management problems presented by these patients. Two recent studies, however, suggest that the incidence of unexpected late complications is not as high as is indicated. Greenland and Howe reviewed the cases of 62 patients with TCA overdose and found no unexpected late complications after signs and symptoms of overdose had abated.[2] The two patients who died in this series had continuing major complications up to the time they died. We reviewed 141 consecutive TCA overdoses and also found no unexpected late events.[3] Six of seven deaths occurred in patients with continuing signs of severe toxicity present from the time of admission. The remaining death was due to pulmonary embolism in an obese patient with only mild signs of TCA toxicity and was presumably due to immobilization rather than a direct toxic effect of the TCA. In this study, patients who had a normal level of consciousness and normal electrocardiogram for one hour did not relapse. It is important to note that all patients had received at least one dose of activated charcoal and a cathartic.

In support of these findings, most patients reported in the literature to have suffered late complications from TCA overdose also had evidence of continuing toxicity at the time of their deaths. Ongoing toxicity was manifested in these cases by prolonged QRS complexes,[4] "abnormal" electrocardiogram,[5] hypotension, coma, isoelectric encephalogram[6] or abnormal neuromuscular activity.[7] These late complications should therefore be regarded as exacerbations of continuing toxicity rather than sudden or unexpected events.

In only a very few reported cases have arrhythmias developed in patients after TCA overdose at a time when other signs of TCA toxicity were absent. One such patient had evidence of preexisting cardiac disease at autopsy, having a dilated heart.[4] The patient described by Callaham, who died nine hours after admission and following an asymptomatic interval, did not receive activated charcoal or a cathartic. As might be anticipated, this patient's plasma TCA concentration increased from 20 ng per ml at the time of admission to 8,600 ng per ml at the time of death and provides an explanation for the observed delayed complications. The potential for delayed absorption from the gut in this situation, as noted by Callaham, is well recognized; peak plasma TCA concentrations may occur as long as 17 hours after drug ingestion in patients who have not received activated charcoal.[8] There is similarly no mention of administering activated charcoal in a report by Slovis and co-workers of two patients who developed sinus tachycardia several days after TCA ingestion.[9] Possible reingestion of drug should also be considered in patients with delayed toxicity accompanied by increasing plasma drug concentrations.

It appears, then, that late complications of TCA overdose are largely confined to patients with continuing

signs of toxicity or those who have not had adequate gut decontamination. Patients at risk for late complitions can be identified and followed appropriately. The occurrence of sudden arrhythmias or death as a late complication in patients without signs of toxicity has not been well documented, and prolonged monitoring of such patients does not seem warranted. The criteria for monitoring suggested by Callaham are reasonable for patients who have ingested any potentially cardiotoxic drug, and are in agreement with previous suggestions regarding the monitoring of patients with TCA overdose.[2,3]

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The PAC-Man Cometh

To THE EDITOR: Jonathan, my 12-year-old grandson, is a Pac-man whiz. He drops in his quarters and deftly manipulates those elusive figures on the TV screen. I entered a mild complaint to his father: wasn't his son wasting a lot of his precious homework time and much of his allowance money? "But don't you understand, Dad," he responded, "that TV's with their computerized brains, are the teaching tools of tomorrow? Anyway, he gets a lot of mileage out of his quarters."

Organized medicine has its PAC-men, as well—a fact not too well recognized by many of our colleagues. In Idaho they go under the name of IMPAC, in California they are CALPAC, nationally they are AMPAC. These political action committees are the skillful manipulators of the figures on the campaign trails and in the halls of the legislatures. Whether we like it or not, that is political reality.

Like Pac-man, who gobbles up his opponents on the TV screen, so do the PAC's take on their political adversaries. CALPAC hobbled the chiropractors, IMPAC has kept the naturopaths at bay and AMPAC has labored long to block various federal agencies from further intrusion into our medical practices.

For those physicians who have been involved in PAC activities, it has been a learning experience. The lesson: our PAC-men make friends and influence people in our state capitals and in Washington, DC. And they get a lot of mileage out of our dollars.

E. R. W. FOX, MD
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Special Editor for Idaho

Additional Sources of Immunobiologics

To THE EDITOR: The list of sources of supply of immunobiologics in the November 1982 issue[1] will be greatly appreciated by physicians striving to manage infectious diseases in the most effective manner. Because of the lack of a centralized medical information retrieval system, such reference lists bridge the literature dissemination gap and provide rapid access to cumulated data. Concurrently with the publication of your list, we were preparing a similar source list of immunobiologics not available through commercial manufacturers. We thought these might be useful addenda to your master list. Each supplier was called twice, most recently in September 1982, to clarify or correct the information previously provided.

SKIN TEST ANTIGENS

Actinomycosis
Not available.

Atypical mycobacteria
Not available; however, under evaluation by the Centers for Disease Control (CDC).

Cysticercosis
Not available.

Sporotrichosis
Not available.

VACCINES

Botulinum toxoid, pentavalent (A,B,C,D,E)
Unlicensed toxoid. Available through the CDC, weekday telephone number is (404) 329-3356; night and holiday telephone number is (404) 329-2888.

Cytomegalovirus vaccine
Not commercially available. Under clinical evaluation by Dr C. Martin, Merck, Sharp and Dohme Co., Inc., West Point, PA 19486, (215) 661-5000.

Eastern Equine Encephalitis (EEE) vaccine
Unlicensed vaccine. Available through the CDC, weekday telephone number is (404) 329-3356; night and holiday telephone number is (404) 329-2888.

Escherichia coli lipopolysaccharide vaccine
Restricted to microbiologists. Available from Difco Laboratories, PO Box 1058-A, Detroit, MI 48232, (800) 521-0851 extension 291.

Pertussis vaccine
Available from Michigan Department of Public Health, PO Box 30035, Lansing, MI 48908, (517) 373-1290.

Pseudomonas polyvalent vaccine
No longer investigated by Parke Davis Company. Although has been under evaluation by Burroughs-Wellcome Company in England, this vaccine is not available in the United States.

Trachoma vaccine
Not available.

Varicella zoster vaccine
Not commercially available but under evaluation by Dr A. McLean, Merck, Sharp and Dohme, Co., Inc., West Point, PA 19486, (215) 661-5000.

Venezuelan Equine Encephalitis vaccine
Unlicensed vaccine. Available through the CDC, weekday

telephone number is (404) 329-3356; night and holiday telephone number is (404) 329-2888.

ANTITOXINS AND IMMUNOGLOBULINS

Western Equine Encephalitis (WEE) immune globulin

Unlicensed immunoglobulin. Available through the CDC, weekday telephone number is (404) 329-3356; night and holiday telephone number is (404) 329-2888.

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Research on Rattlesnake Bites

TO THE EDITOR: I recently had an epitome, "Rattlesnake Bites: Current Hospital Therapy," published in the journal.[1]

As I reread the article in its published form, I note one sentence of possible misunderstanding. On page 411, the last sentence on the page reads "today we have cared for more than 700 persons envenomated by rattlesnakes. . . ." The "we" in the sentence should have been footnoted to include Findlay Russell, MD, PhD. Our research on rattlesnake bites was performed in collaboration with Dr Russell and the majority of the clinical experience comes from Dr Russell and his colleagues at the University of Southern California (Dr Russell is currently at the University of Arizona). I am sorry if any misunderstanding developed because of this lack of reference.

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More on Video Display Terminals

TO THE EDITOR: In the November 1982 issue there appeared a letter by Dr E. R. W. Fox talking about VDT's (video display terminals).[1] He cited a Spokane, Washington, newspaper article dealing with women who had worked with VDT's and had adverse outcomes of pregnancy. In it he makes a comment and I quote, "Yet everyone knows that the cathode tubes and VDT's do emit several forms of radiation." He then goes on to raise the question, "Should VDT operators wear lead aprons?"

As an occupational physician, I must take exception to Dr Fox's reliance on the story from a lay publication. Data do exist regarding these issues. For example, the National Institute of Occupational Safety and Health—the branch of the United States Public Health Service charged with evaluating potential risks in the work environment—issued a report on the subject. It is entitled "Report on Electromagnetic Radiation Surveys of Video Display Terminals." In it, they cite not only their work, but several other studies indicating that the levels of x-ray exposure were in many cases less than the background natural radiation from walls and floors. A number of other researchers have concluded that the emission levels for a variety of forms of radiation are far below any current standards or bioeffects thresholds.

The important consideration is what are the rates of occurrence of various health effects in an exposed population. These must be compared with those of an appropriate control population to see if there is truly an increase. Sporadic occurrences do not necessarily have any significance and are only used for stimulating more definitive research.

Especially in hospitals where these persons had worked, the current data do not seem to support Dr Fox's suggestion that VDT operators should wear lead aprons.

DANIEL F. RUBIN, MD
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REFERENCE

1. Fox ERW: High rock, high tech and Karl Marx (Correspondence). West J Med 1982 Nov; 137:441-442

Action Against Sexually Transmitted Diseases

TO THE EDITOR: Even in our "free" and open society there are topics that are not openly discussed. Chief among these is sexuality. I am sure that this is the reason that we have not faced the epidemic of sexually transmitted diseases in the same way as we are campaigning against a mild childhood illness like measles. True, the press has now caught on and is having fun sensationally bandying about herpes and AIDS (autoimmune deficiency syndrome), but where are the responsible medical authorities and our government?

We physicians, who see, treat and spend so much time with the distraught victims of these preventable diseases, should long ago have demanded vigorous public health intervention and public education. This is not to downplay the dedicated local health authorities who have for a long time fought a good fight with their sleuthing and epidemiological workups. But we know it is not working because the problem is worsening.

Now, we could sit around and blame it all on *Playboy* and *Penthouse*. This in some ways may be right. But that does not solve the already present and worsening problem. I suggest a more general public health and education campaign, which would have the added benefit of helping our citizens to feel more comfortable with the fact that, yes, they are sexual beings. Corollary to this we know that even the more general use of condoms would be of great help.

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Topics in Primary Care Medicine

Urethritis in Men

ELISEO J. PEREZ-STABLE, MD, *San Francisco*

"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

—BERNARD LO, MD
STEPHEN J. McPHEE, MD
Series' Editors

Urethritis is a clinical syndrome characterized by a urethral discharge, urethral discomfort, or both, exacerbated by urination. It is a common outpatient complaint and a major public health problem. Urethritis is a sexually transmitted disease of moderate infectivity, requiring the tracing and treatment of case contacts. Control of the ongoing epidemic will depend upon more rigorous application of this epidemiological principle.

Causes

Two organisms have an established etiologic role in urethritis—*Neisseria gonorrhoeae* and *Chlamydia trachomatis*. *Ureaplasma urealyticum* has been implicated by strong circumstantial evidence, but its definitive etiologic role remains questionable.

Neisseria gonorrhoeae is a Gram-negative, kidney bean-shaped diplococcus that was first described in 1879. In the United States the current yearly case rate of gonococcal infections is estimated at 500 cases per 100,000 population, many of which present as urethritis. Certain groups have an increased risk for contracting gonococcal infections. Black men under 25 years of age of lower socioeconomic status account for approximately 60 percent of reported cases of gonorrhea. Gonococcal urethritis peaks during the summer months, and risk of infection is proportional to the number of sexual partners. Gonorrhea develops in about 25 percent to 50 percent of people exposed to a sexual partner with gonococcal infection. Gonococcal urethritis has a short incubation period ranging from two to ten days. There is no evidence that nonvenereal transmission is important in adults.

Asymptomatic gonococcal urethritis in men is a rare clinical problem. In a city public health clinic population only 0.9 percent to 1.5 percent of asymptomatic men at risk have cultures positive for gonococci, although some recent data suggest this frequency may be higher. This is in contrast to the greater than 80 percent prevalence of asymptomatic gonococcal infections of the pharynx and rectum and the mild nonspecific nature of gonococcal cervicitis. Sexual contacts of patients presenting with disseminated gonococcal infection should be evaluated for asymptomatic gonococcal urethritis, but screening urethral cultures for gonococci in all sexually active men is not recommended—independent of sexual orientation.

Nongonococcal urethritis is defined as the clinical syndrome of urethritis with negative urethral cultures for gonococci (nonspecific or postgonococcal urethritis or pseudogonorrhea). In the developed world nongonococcal urethritis appears to be twice as common as gonococcal urethritis and therefore more likely to be encountered in practice. In the United States nongonococcal urethritis is more likely to be seen in socially advantaged populations—whites, suburbanites, college students—in contrast to gonococcal urethritis. There is no evidence to support a racial susceptibility to one kind of urethritis or another. The incubation period of nongonococcal urethritis ranges from 2 to 35 days.

During the past ten years great strides have been made in defining the etiologic agents of nongonococcal urethritis. *Chlamydia trachomatis* causes an estimated 30 percent to 50 percent of cases of nongonococcal urethritis. In one study *C trachomatis* was cultured from 42 percent of 113 men with nongonococcal urethritis but in only 7 percent of 58 male controls without overt

Refer to: Perez-Stable EJ: Urethritis in men (Topics in Primary Care Medicine). West J Med 1983 Mar; 138:426-429.
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Supported in part by a grant from the Henry J. Kaiser Family Foundation.
Reprint requests to Medical Service (5H-22), San Francisco General Hospital Medical Center, 1001 Potrero Ave, San Francisco, CA 94110.

TABLE 1.—*Diagnosis of Urethritis*

Gram's Stain Result	*Diagnosis*	*Obtain Culture for Gonococci*	*Treatment*
Typical Gram-negative diplococci in the cytoplasm of polymorphonuclear leukocytes	Gonococcal	No	Recommended regimens
No Gram-negative diplococci in any location	Nongonococcal	No	Tetracycline/erythromycin
Equivocal findings	Gonococcal or nongonococcal	Yes	Tetracycline

urethritis. Serologic conversion in culture-positive cases and clinical response to specific antimicrobials have provided further support for *Chlamydia*'s etiologic role.

Another organism implicated as a possible cause of nongonococcal urethritis is *Ureaplasma urealyticum*. In two studies it was cultured in 80 percent of men with *Chlamydia*-negative nongonococcal urethritis; however, in 60 percent of an asymptomatic control group *U urealyticum* also was recovered. Although this difference is statistically significant, a major problem in assigning *U urealyticum* an etiologic role in nongonococcal urethritis is its ubiquity in asymptomatic controls. However, most experts agree that *U urealyticum* may cause nongonococcal urethritis and should be considered in treating this syndrome.

Although several other infectious agents have been postulated as causes of urethritis, none is considered to play a major role. *Trichomonas vaginalis* has been recovered on occasion from symptomatic men but it may represent a coincidental finding. An endourethral chancre of primary syphilis rarely may present as a urethritis syndrome. The common misconception that nongonococcal urethritis is due to excessive alcohol intake or to emotional upset should be discarded.

Clinical Presentation

Urethritis presents with one of two cardinal symptoms: (1) urethral discharge varying in quantity from a small bead of moisture at the meatus to a copious amount sufficient to stain a patient's underpants; (2) dysuria, which is defined as pain or discomfort in the anterior urethra characteristically exacerbated by urination. This discomfort frequently persists between micturition as pain, itching and frequency or urgency of urination, but hematuria and pain on ejaculation are distinctly uncommon. Since urine may clear the urethra of a slight discharge, examination should be carried out at least two hours after urination for optimal yield. If a spontaneous discharge is not apparent, stripping the urethra results in an exudate in more than 90 percent of remaining cases of urethritis.

Gonococcal urethritis presents most commonly with dysuria *and* a copious, spontaneous purulent discharge. In contrast, nongonococcal urethritis is more likely to present with dysuria *or* discharge, with as many as 20 percent of patients having no expressible discharge despite penile stripping. When a discharge is found it is more often mucoid than purulent and small in quantity. Since nongonococcal urethritis tends to be a milder clinical syndrome the majority of patients present more than four days after the onset of symptoms; the opposite is seen with gonococcal urethritis. In both gonococcal and nongonococcal urethritis local complications include epididymitis, prostatitis and urethral stricture; systematic complications may manifest as disseminated gonococcal infection or Reiter's syndrome.

Diagnosis

The differentiation of gonococcal and nongonococcal urethritis on clinical characteristics alone is difficult. A Gram's stain of the urethral discharge provides a simple, unequivocal, inexpensive and rapid method of differential diagnosis in most cases (see Table 1). Findings from a Gram's stain of a urethral discharge are abnormal if at least four polymorphonuclear leukocytes are seen per high-power field.

When typical Gram-negative diplococci are found within the cytoplasm of polymorphonuclear leukocytes, this is diagnostic of gonococcal urethritis. In large series this finding correctly identifies 90 percent of gonococcal urethritis cases and this Gram's stain finding has a positive predictive value of 98 percent using a positive culture as the gold standard. It is recommended, therefore, that therapy for gonococcal urethritis be instituted on the basis of this Gram's stain finding alone without carrying out an initial culture. A follow-up test-of-cure culture is recommended in all these patients.

A Gram's stain of urethral exudate showing *no* Gram-negative diplococci in *any* location (intracellular or extracellular) excludes gonococci as the cause of urethritis in 98 percent of cases. Routinely culturing for *N gonorrhoeae* in this situation is not recommended and appropriate therapy for nongonococcal urethritis should be initiated.

Results of a Gram's stain of urethral exudate are equivocal when it shows typical Gram-negative diplococci in an extracellular location only or atypical pleomorphic Gram-negative diplococci in any location. This situation requires further evaluation by culture in order to exclude a gonococcal cause. In one series 25 percent of 65 Gram's stains that gave equivocal findings were culture positive for *N gonorrhoeae*. Thus it is recommended that in equivocal cases cultures for gonococci be obtained and empiric therapy with a tetracycline be initiated.

The excellent sensitivity and specificity of Gram's stains as a diagnostic test in urethritis are derived from sexually transmitted diseases clinics. In the office setting where a Gram's stain may be done infrequently these characteristics of the test may not hold true. As a result a greater number of equivocal findings on Gram's stains requiring culture for gonococci is to be expected in

TABLE 2.—*Treatment of Urethritis—Summary of Adequate Drug Regimens*

Drug Regimen	*Gonococcal Urethritis*	*Penicillinase-Producing* Neisseria gonorrhoeae	Chlamydia trachomatis	Ureaplasma urealyticum	*Incubating Syphilis*
Aqueous procaine penicillin G 4.8 million units IM + probenecid 1 gram orally	Yes	No	No	No	Yes
Ampicillin 3.5 grams or Amoxicillin 3.0 grams + probenecid	Yes	No	No	No	Yes
Spectinomycin 2 grams IM	Yes	Yes	No	Partly effective	No
Tetracycline 2 grams for five days	Yes	50% Failures	Yes*	Yes*	Probably effective
Erythromycin 2 grams for five days	25% Failures	Unknown	Yes*	Yes*	No
Trimethoprim-sulfa 9 single-strength tablets for three days	Yes	Yes	Yes*	No	No
Cefoxitin 2 grams IM + probenecid	Yes	Yes	No	No	Probably effective
Cefotaxime 1 gram IM	Yes	Yes	No	No	Probably effective

*Treatment required for 7 to 14 days.

situations where there is less experience with the test.

Urethral specimens for cultures for *N gonorrhoeae* should be obtained with a calcium alginate swab inserted at least 2 cm into the urethra. For optimal yield this should be immediately plated on a modified Thayer-Martin medium. Cotton swabs are very uncomfortable and cotton may be toxic to some strains of *N gonorrhoeae*.

Isolation of *C trachomatis* requires tissue culture that is not readily available. In addition, it is expensive and results are usually delayed for about a week. Serologic diagnosis can be made retrospectively with the sensitive microimmunofluorescent techniques, but these have similar disadvantages to tissue culture. Given the currently available methods it is not practical to culture routinely for either *C trachomatis* or *U urealyticum*. Thus the diagnosis of nongonococcal urethritis is based on the exclusion by Gram's stain and culture of gonococcal causes; serology or other cultures to confirm this diagnosis are not recommended.

Therapy

The treatment of urethritis is summarized in Table 2.

The choice of drug regimen for uncomplicated gonococcal urethritis is primarily determined by the presence or absence of a history of penicillin allergy. Probenecid should be administered with each of the penicillin regimens in order to attain adequately high levels of penicillin. All of the listed regimens are equally effective for gonococcal urethritis but variably effective for coexistent pharyngeal and rectal *N gonorrhoeae*.

Penicillinase-producing *Neisseria gonorrhoeae* (PPNG) has been reported since 1975. It now constitutes a major problem in several Asian countries and may soon have a worldwide impact. In the United States its prevalence remains at less than 1 percent in most states, with most cases linked to contacts in East Asia. From 1979 to 1981 the number of reported cases caused by penicillinase-producing *Neisseria gonorrhoeae* increased ninefold with localized outbreaks in Los Angeles and Miami. In order to maintain adequate surveillance of such cases in the United States it is recommended that (1) all cases of gonococcal urethritis have a test-of-cure culture three to seven days after completion of antimicrobial therapy and (2) all treatment failures of gonococcal urethritis be confirmed by culture, checked for penicillinase production and treated with an effective regimen for penicillinase-producing *Neisseria gonorrhoeae*. Recommended antimicrobial regimens for this type of urethritis include the following: spectinomycin, 2 grams intramuscularly; trimethoprim-sulfa, 9 single-strength tablets a day for three days, or cefoxitin, 2 grams intramuscularly plus probenecid, 1 gram orally. Tetracycline is effective in only 50 percent of penicillinase-producing *Neisseria gonorrhoeae* infections and it is not recommended as empiric treatment. The third generation cephalosporins are effective in the therapy of gonococcal infections including penicillinase-producing strains. At this time the only patients with gonococcal urethritis who should be empirically treated with an effective regimen for penicillinase-producing strains are (1) contacts to a known case of infection with these strains and (2) cases following recent sexual contacts in East Asia.

Treatment of nongonococcal urethritis is empiric and based on exclusion of a gonococcal cause. Tetracycline given for at least seven days will cure 80 percent of *C trachomatis* urethritis and 70 percent of presumed *U urealyticum* urethritis. Erythromycin is effective against both *C trachomatis* and *U urealyticum* but it has a 25 percent failure rate against gonococcal urethritis. Sulfonamides are effective for *C trachomatis* urethritis but ineffective against *U urealyticum*. Penicillin is effective against neither *C trachomatis* or *U urealyticum*. Thus 2 grams of tetracycline per day for seven days is the recommended therapy for nongonococcal urethritis. A regimen of 2 grams of erythromycin per day for seven days is recommended as an alternative for tetracycline intolerant patients and cases of treatment failure. In up to 30 percent of patients with nongonococcal urethritis, therapy will fail or relapse will occur within seven weeks; a second course of antimicrobials and sympathetic follow-up by the primary care physician will be needed.

It is imperative to treat the sexual contacts of cases with gonococcal urethritis with appropriate antimicro-

bial drugs regardless of the presence or absence of symptoms. The treatment of sexual contacts of cases with nongonococcal urethritis is as yet an unresolved issue. Correct use of condoms has been reported to protect men from gonococcal urethritis but this assumption cannot be made in treating case contacts. It is the physicians' responsibility to pursue contact tracing with the cooperation of patients and the assistance of public health departments.

Summary

Urethritis is a frequently encountered clinical problem with an important differential diagnosis. Gram's stain of urethral discharge can determine its cause quickly in many cases; culture for gonococci provides complementary information in cases with equivocal Gram's stain findings. Therapy for gonococcal urethritis is effective with any of several regimens but special attention should be given to possible infections with penicillinase-producing *Neisseria gonorrhoeae*. Nongonococcal urethritis is best treated with tetracycline or erythromycin. All sexual contacts of patients with urethritis of any cause need to be evaluated and treated.

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Cross-cultural Medicine

Multiple Causality: Consequences for Medical Practice

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When a scientifically trained health professional is called upon to deal with patients holding differing causal views of illness, the resulting lack of communication is frustrating to both. This discussion traces some implications for medical practice of significant cultural differences in two aspects of causal paradigms of illness: (1) terms accepted and (2) dimension or level of causality typically sought. The second is the more pervasive and intractable problem, having distinctive consequences for the role of curer, symptomatology, diagnosis and treatment.

Modern medical scientists are apt to be ethnocentric about causality, assuming that questions and statements about causes have only one meaning which is self-evident and general. This is not the case. Causal thinking is socially determined. That is, notions as to what constitutes an adequate causal explanation are as rooted in the perspectives of each society as are its ideas of right and wrong. Nor, as history shows, are such notions fixed: ideologies and technologies change through time and the meanings of "cause" change with them.[1,2] Closer to home, we find that causality is also relative to disciplinary stance and to the nature of the problem at hand: like maps, "the sort of explanation which is appropriate for one purpose is not appropriate for another."[3] And even within our own medical tradition, many issues in causal attribution remain problematic.[4]

The practice of medicine is dependent on a two-way flow of information. Causal relativity is consequential for this process insofar as a physician's patients do not share his scientific perspective.[5] This is most obviously the case when patients are members of societies outside the Western tradition. But we need not go so far afield: it is also true for many ethnic and even mainstream members of our own society.[6,7] When a scientifically trained health professional is called upon to deal with a patient holding differing causal views, the resulting lack of communication is frustrating to both.[8,9]

The problem is not one of divergent logics, for logical processes are the same the world over. What differs are aspects of the causal paradigm: the elements (or terms) considered appropriate in explanations, and the levels of cause appropriately addressed.[10-13] Obviously, what is *appropriate* is the content on which logic operates, not its structure. Nevertheless, such content differences are fully capable, in themselves, of wreaking havoc in medical practice.

Causal Paradigms

Questions about cause* are fundamental to human thought. Work in cognitive development[14,15] suggests that Kant correctly attributed the notion of cause to the structure of the human mind itself. Put simply, we are unable to conceive of an event that has no cause. We may do no more than wonder what the cause might be, but we are sure that there *is* one. Beyond this, the question of cause is no longer simple.

To ask about cause is ambiguous and may include any of a number of questions. The most basic and universal are *why* (What is responsible? What is the purpose?) and *how* (In what manner did this event occur?). Throughout centuries of philosophical debate, causal distinctions and classifications have multiplied, along with technical terms. To avoid misunderstanding, we will follow the usage of anthropologists such as Peck[16] and Clark[17] and refer to the determination of final responsibility or purpose as *ultimate cause* (the *why* questions) and the mechanics of occurrence as *immediate cause* (the *how* questions).

Although ultimate and immediate causes can be con-

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sidered different dimensions of causality, they also appear as different levels of explanations sought. For example, do we accept a bacterial invasion as cause of an illness and seek no further? Or do we ask why the infection occurred? If we succeed in determining the circumstances of infection, do we go on to ask why those circumstances occurred? Do we ask about purpose? The questions can go on and on. The point at which we stop, satisfied by the level of explanation reached, is primarily determined by the causal paradigm we have learned to apply to this particular kind of event. Within modern medicine, for example, one specialty often begins its causal questions at the point where another stops (epidemiology and bacteriology, for example). Every paradigm, tacitly or explicitly, targets a preferred level of causal explanation for specific classes of events, and in general places relatively greater emphasis on ultimate or immediate cause.

The purpose here is to trace out some of the implications for medical practice of significant cultural differences in both aspects of causal paradigms of illness: (1) terms, largely immediate causes, that are acceptable (viral infection versus demonic possession) and (2) dimension or level of causality typically sought (immediate versus ultimate). The second is the more pervasive and intractable problem.

Immediate Causes of Illness: The Question of How

Every culture recognizes antecedent-consequent relations: the familiar "If *X*, then *Y*." But there are major cultural differences as to which *X*s are permitted and which mechanisms are acceptable to relate *X* and *Y*. These terms and mechanisms are bound into models which, at the same time, *both explain and define reality*. The scientific paradigm, for example, typically delimits its reality to material terms and restricts causal relations to antecedents operating through measurable mechanisms such as chemical reactions.[18]

As the history of science documents, discovery of new mechanisms may alter prevailing concepts of cause, hence the reality defined by the paradigm. Explanations of electricity and radioactivity, for example, each modified our concept of matter and expanded our repertoire of causal mechanisms. And so our perspectives changed, by which we mean—in a literal sense—that we see a different world.

However, as Kuhn[19] showed, paradigms are inherently conservative. Faced with inexplicable data, the tendency is to reformulate them to fit, or to reject them outright. For example, claims of deaths by witchcraft and control of autonomic processes by yogis were initially rejected because they could not be fitted into the prevailing scientific paradigm. As new mechanisms were discovered and brought into the paradigm, states of mind could be rephrased in these terms and the claims accepted. (A current instance of this process is the scientific community's investigation of acupuncture. If an acceptable mechanism can be found—that is, one which fits into our paradigm—the claims for acupuncture can be assessed without the cognitive discomfort so apparent today.)

The point is that all paradigms limit and shape reality. "Perception of what is believed to exist develops into existential propositions."[20(p503)] Reality is the consensus of a group's learned perceptions—we never simply "see it as it is." When dealing with alternative (that is, nonscientific) medical practices, little sense can be made of them unless we make an effort to understand their underlying premises and models. Since excellent analyses are available of an array of causal terms in paradigms other than our own,[21-24] we will give only one example to illustrate the medical consequences arising from the widespread concept of soul loss.

Soul Loss

In many cultures humans are assumed to have one or more souls which can temporarily be lured or driven out of the body with various consequences to health. Among the Ilocano (Philippine rice-farmers) the soul leaves the body under conditions of fear, shock or intense longing, as in homesickness. Children's souls, being less firmly seated than adults', are easily dislodged by even moderate stress levels.[25] Soul loss causes tremors, tics, dizziness, fainting, delirium and coma—interruptions of normal consciousness and control (the Latin American ailment *susto* is felt to have a similar cause).[26]

Soul loss occurs in a paradigm which includes detachable souls and a mechanism of mystic bonding to place or person. This paradigm underlies all aspects of soul loss as a medical syndrome. For example, since both patient and practitioner regard soul loss as a likely cause of a child's illness, they will focus on symptoms of interrupted consciousness to the neglect of other symptoms such as fever, pallor and rigidity. This focus encourages the grouping of all loss of consciousness symptoms into one diagnostic category, presumed to have the common cause of soul loss. Due to the nature of this cause, the treatment indicated is to lure the soul back into the body by techniques that weaken the mystic bonds.

Given the terms of the paradigm within which these symptoms are perceived, both diagnosis and treatment are appropriate and rational. Of course they are "magical." So is our x-ray to an Ilocano villager. Magic is a contextually determined term and has little to do with rationality, but has everything to do with conceptions of reality.[27,28] We might define magic as a technology based on another's reality.

When two disparate versions of reality meet, confusion and miscommunication can be expected. A patient, certain his illness is soul loss, cannot understand the Western doctor's insistence on secondary symptoms and irrelevant data. The doctor, pressing for full description of symptoms and background as his paradigm requires, cannot understand the patient's reluctance to provide information. Diagnoses and recommended treatments made under these conditions are often re-

jected, to the doctor's bewilderment and annoyance. Misunderstandings lead readily to mutual charges of incompetence on the one hand and superstition on the other, vitiating further attempts to provide and obtain medical care. When the second paradigm difference—dimensions of causality—enters the picture, difficulties are multiplied.

Ultimate Cause of Illness: The Question of Why

The likelihood of a structural basis of causal thought emphasizes the primacy of ultimate cause questions. A child's first question about cause is *Why*? And it is first answered in purposive terms: it rains to make the flowers grow; the car moves to take us for a ride. Cause is ultimate purpose. However, the distinctive feature of modern science has been the extent of radical delimitation of causal paradigms to immediate causes. Therefore a large part of growing up in our society is learning appropriate cause statements; that is, learning to answer questions about cause by specifying chains of immediate antecedent-consequent relations. Ultimate, purposive causes have been relegated to religion or philosophy as nonscientific issues.

Medically, this means that when a patient asks *why* he is ill, he receives an answer about *how* he became ill. Since modern medicine has identified an impressive array of causal sequences, the scientist feels he has provided a satisfactory answer. In contrast, most systems of medicine outside the Western tradition do not limit themselves to immediate antecedents, but go beyond them to deal explicitly with other aspects of cause.* Typically the emphasis is more often on ultimate causes than on immediate. In such systems, the manner in which an illness has developed is assuredly of interest, but *why* it occurred is of paramount importance.[29,30]

A scientist is likely to explain this difference of focus by lack of knowledge, the inability of other systems to accurately account for the causes of most ills. According to this line of reasoning, if naturalistic explanations of illness were understood, there would be no need to search for ultimate cause. This argument presumes that "scientific" answers are satisfying to the Western patient and ultimate cause questions are no longer asked. In fact this is by no means the case: patients continue to ask the purposive *why?* Modern medicine abjures the question, but it does not vanish when ignored. The answer is simply sought outside science.

For years, a related and more exotic difference has received the bulk of the attention—that of personalization. Developmentalists have shown that the young child's world is a personalized world wherein virtually all objects are motivated, hence causes are predominantly purposeful agents.[14] By maturity, personalizing has been reduced to socially acceptable levels and purpose as cause is now attributed only to those things that can be personalized, hence can have motives. Currently, modern Western usage limits personalizing to animate things, primarily humans; therefore purposive cause is also so limited.

In contrast, many other cultures allow more latitude in personalizing their worlds; purpose as cause need not be limited to humans. Therefore it is common for illness to be attributed to persons (witches, ghosts) or personalized forces (gods, spirits) working by means of various immediate causes. These mechanisms, however, may be either supernatural or naturalistic.[31,32]

However, it is easy to become distracted by this issue. *In itself,* the attribution of personal motivation to forces we regard as inanimate is not necessarily consequential. It is the level or type of cause typically sought that is the more important determinant of the nature of a medical system. For example, although many systems do assume the existence of purposeful agents, this is not the case in a number of traditions that see illness as the outcome of disturbances of equilibrium—within the body, between body and soul or between self and the social or spiritual order.[9,33,34] In such systems, depersonalization is often the rule. Nevertheless, the search for ultimate causes of disequilibrium has had far-reaching consequences which have resulted in medical systems very different from our own.

Popular accounts have made us most familiar with dramatic contrasts in treatment: chemotherapy versus incantations, penicillin versus purgatives. But the search for ultimate causes influences the entire system, from professional training through diagnosis. The following discussion will emphasize these less publicized, but even more consequential, influences.

Medical Professionals

In some respects all professional curers (including Western physicians) are similar. On the curer's part, this role entails the apprehension of forces at work that are obscure to laymen, intense and sustained efforts to cure ills, and high social status if successful. On society's part, there is esteem mingled with fear of possible misuse of special skills. In most systems other than our own, the curer's role is distinctive because he also accepts determination of ultimate causes as a *medical* problem, thus as a necessary part of his job. Within such paradigms this is commonsense practicality: in cases of spirit-induced illness, for example, the important question is not *how* this is accomplished, but *what* is responsible. If this cause is not combatted, the patient cannot be permanently cured and will suffer attack after attack.

Since causal agents are often spirits, forces of nature or witches, the curer then must deal with potent and dangerous forces in order to mediate between patients and the sources of their ills. In addition to whatever secular skills he possesses, his role demands supernormal power. Such power may be acquired in various ways, depending on cultural rules and curer's specializations,

*Secular medicine (drugs, massage, ointments and the like) is well developed in most medical systems, but because it is directed primarily toward simple symptom alleviation and unambiguous causes (exposure to cold, muscle strain), it will not be dealt with here. The interested reader can find many references in Landy.[23]

but teaching alone is not enough. Power may be inherited, be induced by drugs, trance or fasting, and be even unbidden, imposed by spirits. However it may be acquired, the power is outside the normal and in the realm of the sacred.[35] This distinction between curers and lay specialists in secular practice is clear in the following accounts of the source of the skills of two Ilocano professionals:

- Midwife (secular practitioner):

Anyone can be a midwife if they have the patience to learn, though it is true some are better at it than others. I was taught by an old woman. . . . She helped me at first, but gradually I did more and more. (C. N. Nydegger, PhD, unpublished data, 1956).

- Curer (sacred practitioner):

Pacifico ran home as if crazy, hitting anyone in his way. His neighbors caught him and took him to his house where they tied him, while he struck out and shouted. He continued like this for some time, fighting with the *not-humans:* he was afraid and did not want to accept the relationship. Finally he surrendered to them and became normal again—for if you do not give in they may cause your death—and he became a well-known curer.[36(p74)]

Because causal agents are often supernatural and a curer's role is then analogous to a priest's, it has been claimed that such medicine is confused with religion.[29,37] But this is true only if we insist on our occupational boundaries. From a curer's perspective, he is practicing medicine whatever we call it. It is interesting, in this regard, to note that when various shamanistic practices were shown to have therapeutic value for mental illness, we began to call these activities "curative" rather than "religious." In common with all cultural categories, "medicine" and "doctor" are in the mind of the beholder.

Symptoms

Symptoms enter into a medical system at two levels: a patient's use of symptoms to determine his need for medical attention, and a professional's use of symptoms in diagnosis. Out of all the fluctuating physical sensations and mental states that bombard the patient's consciousness, he selects out only a few as signs of malfunction, of illness. How is this screening accomplished? What criteria are employed?

Overwhelmingly the criteria are cultural, learned in relation to specific paradigms of illness. This subject is difficult to discuss, for our terminology implies a good deal more than is useful here. The phrase *symptom recognition* is commonly used to refer to a patient's awareness of a medically relevant condition. However, *recognition* implies that a "real" symptom is present, of which the patient becomes aware. But the process actually is that of *creating* a symptom by selecting out certain sense-perceptions which are then labeled "symptom." Selection occurs in relation to a specific paradigm and is meaningful only in relation to that paradigm. With illness as with other troubles, "the effort to find and implement a remedy is critical to the processes of organizing, identifying, and consolidating the trouble."[38(p122)]

Symptom labeling is no more than the familiar process of labeling any sense-perception, which involves learned categories and learned criteria of inclusion. That such categories differ from culture to culture is now well known. Although the spectrum, for example, is apparently perceived as such universally, the color categories into which it is divided differ arbitrarily (that is, one group's blue may include another's green, and so forth). The aspect of labeling of importance here is its relation to paradigms. A simple example is the tomato: is it a fruit or a vegetable? Necessarily, the answer is "it depends." It depends on the context of discourse and on higher level constructs of function, which give meaning and specify the conditions under which something is a fruit or vegetable.

In this fashion, symptoms depend on constructs and paradigms of illness. Many factors enter into symptom labeling. Simple frequency has been repeatedly documented as one such factor: some disorders are so ubiquitous that they become normal for these populations and those not so afflicted are seen as abnormal.* More subtle sociocultural factors have also been shown to be important: health values, cultural emphases on certain portions of the body, use of denial and so on.[6,41] The effects on this process of differing constructs and levels of causality in medical paradigms have been neglected in this literature, yet they are basic and consequential.

We begin as children to learn to label specific sensations as symptoms: "I have a stomachache. I feel feverish." We also learn (albeit often incorrectly) which symptoms are minor and can be dealt with at home and which are serious and should be brought to a practitioner's attention. Cultural models of illness select some conditions as important, but not others. The selected conditions are gradually learned *as symptoms*. For example, Americans take temperatures because they have learned that fever is a symptom, although they may not know precisely of what. The Ilocano immediately label any swelling as a symptom (of probable witchcraft), but fever may be ignored until it is extreme.

When the medical paradigm emphasizes ultimate cause, illness categories are more often defined in these terms than by immediate cause or physical sensation (witchcraft rather than inflammation, for example). Symptoms are therefore less often illness-specific[42] and are of secondary importance to patient and curer alike. A relative lack of interest in symptomatology is pronounced in cultures like the Navajo, whose medical paradigm is an equilibrium model. For a Navajo patient, any persistent discomfort is a sign of discordance and disequilibrium, be it depression, chest pains or aching joints. The presenting symptom commonly takes the form "I feel bad all over." This is perfectly clear to a Navajo diagnostician who initiates a search for cause of the disturbance. Neither patient nor curer need pursue symptoms further.

In accordance with this causal paradigm, a Navajo patient has been taught to discriminate only a crude

*For example, Ackerknecht[32] reports this for a skin disease in South America, Wallace[39] notes a similar acceptance of hallucinations and Clark[40] reports ignoring of coughing, sweating and children's diarrhea.

vocabulary of symptoms. Nor does he see the need for further refinement, since the problem is ascertaining *why* an imbalance has occurred; with a few exceptions, symptoms are irrelevant to this problem. However, a physician finds "feeling bad all over" an inadequate description and cannot understand why his requests for further specificity are met with incomprehension.

There is a two-way flow of influence between diagnostic categories and symptom labeling. Contrary to textbook organization, our symptoms are shaped by our culture's diagnostic categories and by the causal bases of our medical paradigm. When lay and professional paradigms are essentially the same, symptom labeling is similar; patient and practitioner speak the same medical language. But when paradigms differ, miscommunication typically results even at this initial contact, setting the stage for further difficulties.[43]

Diagnosis

In all medical systems, treatment is determined by diagnosis. But when the system emphasizes ultimate causes, determination of the process (immediate cause) is of secondary importance, if not irrelevant. In this context, constellations of symptoms tend to be unreliable diagnostic criteria. In the first place, symptoms are often ambiguous, pointing in many directions. Second, the powers of the supernatural are broad: if such an agency is responsible, the same syndrome can take many guises. Third, even unambiguous ailments may not provide causally diagnostic answers; for example, smallpox is often thought to be spread (caused in the ultimate sense) by supernaturals.[36]

Background information is a major source of diagnostic hints for all medical practitioners. But an indigenous medical history bears little resemblance to that obtained by a physician, although it is a functional equivalent. The latter's interests are in childhood illnesses, symptom lists and the like—a narrow focus on the patient himself. The indigenous curer is more often concerned with such things as breaking of taboos, working in spirit-haunted places, bad relations between neighbors—a broad picture of the patient in his social context. The two kinds of histories converge mainly in determining sources of infection or poisoning when questions of work and leisure habits, social contacts and movements are also pertinent within the scientific paradigm.

Patients are accustomed to certain kinds of questions, which make sense to them within their own models of illness; they understand that they are diagnostically relevant, though they may not know why. So we expect questions about our health history, but not about dislike of our in-laws. The indigenous patient understands his curer's need to know where he has been cutting wood (to estimate probabilities of angering wood spirits), but he is unlikely to see the point of questions about a swelling-in-the-neck illness in childhood.

Diagnosis is even more difficult for indigenous curers than for our own professionals. First, symptoms and illness categories are less useful, for the curer is charged with determining ultimate causes. Although medical histories may limit possibilities, they are unequivocal only in cases of flagrant transgression of taboos. Second, instances of apparent causes masking deeper causes are not uncommon; a diagnosis may be correct yet inadequate because it did not reach the ultimate cause. Third, diagnoses of witchcraft and taboo breaking often involve members of the patient's family or community. A faulty diagnosis in these cases can be more dangerous to curer than patient.

Fourth, if supernatural agency or witchcraft is suspected, the sacred power of the curer is prerequisite for diagnosis itself. Only trance, divination—some beyond-normal experience—can lead to correct causal attribution. Whether the curer's medical paradigm is elaborate[8,44] or relatively simple,[36,45] the majority of diagnostic decisions are based on contact with the sacred,[30] always a source of potential danger to the curer. This ingredient of diagnosis is emphasized in systems like that of the Navajo, who have placed diagnosis and treatment in the hands of different specialists. Treatment skills involve ritualized contacts with supernaturals, which are taught during a lengthy apprenticeship. Diagnostic skill, on the contrary, is unteachable: it is an inherent ability to divine, merely refined by practice.

However accomplished, diagnosis is never idiosyncratic or unsystematic. It too is shaped by the general cultural context and constrained by the medical paradigm within which it occurs.[46-48] The range of diagnoses for broad classes of illness is always limited and the curer whose diagnoses deviate notably from this pattern is suspect. These diagnostic patterns may appear unsystematic: sometimes they refer to the immediate cause (such as soul loss), at other times to purposefully causal agents (witchcraft) and even to Western disease categories (smallpox). But underlying the apparent confusion is a paradigm-related orderliness which becomes apparent when we focus on the question of ultimate cause—*why* rather than *how*.

Treatment

"Hierarchies of resort" in curative practices have much in common the world over.[34,49-51] In every society known, mild symptoms and common ailments are first treated by home remedies. Poultices and potions are universal; heat treatments and massage are widespread, as is prayer for supernatural intervention. Indigenous lay medicine also has remedies to deal with minor ills that have supernatural causes: charms, rituals, incantations and the like. Contrary to popular assumption, not all supernaturally caused ills are grave or mysterious; they may often be diagnosed and cured by home remedies with no more fuss than we make over a cold. In a mild case of children's soul loss, for example, simple incantations and object-manipulation can neutralize the bonding mechanism and lure back the soul.

However, if lay medicine provides no relief, or if the symptoms are ambiguous, professional diagnosis and treatment are indicated. (These days, one of the pro-

fessionals consulted is likely to be a Western physician. The conditions under which he or she is consulted have been studied in many societies.[22,52-57])

The distinction between secular and professional medicine cannot be reduced simply to treatment modalities, of naturalistic versus supernatural (for example, massage versus ritual). Both are present in most curing, be it lay or professional. The professional's treatment is distinctive in that he either has special knowledge (modern physicians, Navajo singers) or sacred power (Ilocano curers) not shared with his fellows. Thus everyday remedies and common substances may be transformed or embellished in medical treatment, for the distinction is not of modality, but of provenance and power. For example, in one treatment an Ilocano curer used six sacred and six secular elements.[36(p87)] But treatment, like diagnosis, is constrained by its cultural context: societies accept a limited range of treatment patterns. The curer is not free to invent at will, though he may embellish traditional treatments in highly individual ways.

The purpose of treatment is to cure—a layman's term, vexatious to define and one that has been discussed much of late. We would expect cases of total remission of symptoms to qualify as cures in any system. But this is not certain. Take a simple fracture resulting from a fall: after a clean mend, a Western patient considers himself cured. However, an Ilocano patient would be uncertain: might not the fall have been caused by angry spirits? Do they remain unappeased, perhaps waiting to do another injury? The curer accepts this possibility as a *medical* problem and, as an integral part of his treatment, sees to it that appropriate steps are taken to forestall the danger. Similarly, a Navajo patient, although freed of specific symptoms, may remain convinced that something remains out of balance in his world, threatening further illness. Until the appropriate rituals are performed, his cure is not complete. Thus decisions as to what constitutes proper treatment and when a cure is completed are determined as much by causal notions as by physical state.

Conclusion

Indigenous systems of medical belief are complex and varied, but even this brief discussion shows the important consequences of differing causal notions. Not only do causal terms of medical paradigms vary among systems, but the target levels of cause differ. Most of the world's medical systems try to answer questions about ultimate causes, entailing distinctive consequences for the professional's role, symptomatology, diagnosis and treatment.

Although indigenous and scientific perspectives are not necessarily antithetical, they commonly talk past one another, resulting in confusion and misinterpretation. Only if we understand an Ilocano curer's perspective can we understand his equating of modern Western and traditional Chinese doctors: "Their medicine is piercing with needles. I do not use this . . . I talk with the spirits" (C. N. Nydegger, PhD, unpublished data, 1956). Since both deal merely with efficient causes, they are scarcely worth distinguishing from one another.

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Medicine in Perspective

On Privileged Communication: A Comparative Study of Several Medical Cases

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And whatsoever I shall see or hear in the course of my profession, as well as outside my profession in my intercourse with men, if it be what should not be published abroad I will never divulge, holding such things to be holy secrets.[1(p301)]

Every physician will recognize this exhortation as a quotation from the Hippocratic oath. It is one of the few statements that has not been hotly debated as to authenticity or justification. It means, in the words of the translator and interpreter W. H. S. Jones, "The physician must not gossip, no matter how or where the subject matter for gossip may have been acquired; regardless whether it be in practice or private life."[1]

With this comment, Professor Jones goes beyond the original injunction. He excludes all manner of gossip from the physician's repertoire of conversation, whereas the oath itself restricts as secret only "What should not be published abroad."

In this fashion, Jones interprets the injunction somewhat like the Chinese code of medical ethics, which is of uncertain date and authorship and probably stems from an aphoristic compilation of Sung dynasty (tenth century) writings. Here we read, "Examine the patient carefully and never speak of what you experience in his house not even to your wife."

No one can tell with an assurance what was the actual relationship of the Hippocratic oath to the totality of the *corpus hippocraticum*. In fact, as Professor Jones states, this relationship is "unknown and, indeed unknowable," although Edelstein, on the other hand, offered specific theories.[2] We also do not know how representative the oath was of Greek thought; whether it was taken by all the practitioners of medicine, or perhaps only by the members of a select medical guild. Besides, it is unknown whether the oath had a binding force beyond its moral sanctions: Was it taken literally as an oath, or simply interpreted as—again in Jones' words—"a counsel of perfection"?

In China the injunction of the ethical precepts was hampered by the peculiar way in which in former times physicians were selected: In our way of speaking they were given a chance to "make a bid" for the patient; several physicians were invited to examine the patient, make a diagnosis and suggest a specific therapy, and the one was retained whose diagnosis and therapeutic suggestions were most pleasing to the patient, to his family or to his friends. In such a procedure many more than "the doctor's wife" became familiar with the patient's illness and the goings-on in his house.

Taken literally, the Hippocratic oath, as well as the Chinese code, deprive the physician of a most tempting subject of conversation. But, somehow, although few among the public know of the oath, or the traditional injunction to medical discretion, it is taken for granted that whatever goes on between the patient and his doctor assumes a state of privileged communication, similar to that with a lawyer or a priest and they react with dismay at the breach of silence.

If we wonder, whether the details of the oath have any noticeable influence upon doctors of today, we are interested to see if physicians in earlier times actually abided by the injunction of privileged communication.

Transgressions of the rule of privacy can rarely be found in the writings of Hippocrates, since case histories had not yet come into general use. In those few histories in *Epidemics* in which names were mentioned, a tendency towards anonymity is perceptible. The few individual patients listed are devoid of identification as to their age, local origin and family so that scarcely any conclusion as to their identity could have been drawn.

Later, in the Greco-Roman antiquity, in the second century AD, we find that Galen of Pergamon, although a devout admirer of Hippocrates, could not resist the temptation inherent in being physician to the intellectual and imperial elite. His case histories on the illness and recovery of Emperor Marcus Aurelius and the famous peripatetic philosopher Eudemus appeared in full detail. That in both cases Galen's own opinion and regimen had differed sharply from those of his colleagues added considerable spice to the pleasure in his disclosures.

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However, it needs to be stressed that Galen's revelations concerning the illnesses of these prominent patients were directed not to the general public but to other physicians who were presumably bound by the code of professional confidence.

There have been, of course, other medical men in history who could not resist the temptation of writing detailed descriptions of the illness and final days of illustrious patients. Such physicians incurred severe criticism for what the world of their contemporaries considered blatant indiscretion. This criticism sharpened, because some publications expanded beyond the purely medical aspects and included descriptions of the patient's political life, as it was influenced by the course of his illness. Specific examples at hand are the two histories that were written about the last illness of King Frederick II of Prussia and the publication of excerpts from the Diary of Lord Moran, as they refer to his observations of his eminent patient, Sir Winston Churchill.

Dr C. T. Selle

The personality and illness of the Prussian king were so striking that they gave rise to two monographs from the pens of the last two physicians who attended him. One appeared in 1786, the year of Frederick's death, in several installments in a Prussian medical journal, entitled *Neue Beiträge zur Natur- und Arznei-Wissenschaft*,[3] a publication designed for medical scientists, to which lay readers and court gossips did not normally have access. The author of this monograph was Dr C. T. Selle, Professor of Medicine, physician to the Charité Hospital and member of the Royal Academy of Science at Berlin. Dr Selle had been one of Frederick's several personal physicians who had been replaced by the more flamboyant and famous Dr Johann Georg Zimmerman, a compatriot and student of Albrecht von Haller. After an honorable and successful career in his native Switzerland, Zimmermann had been called to the Royal Court at Hanover to become personal physician to the King of England, George III. It was from Hanover that Frederick the Great called Zimmermann to his sickbed in Potsdam, as he expected that the famous Swiss physician might be able to restore his sadly deteriorated health.

In this expectation he was mistaken. The art of medicine of the 18th century was powerless to cope with the king's complex ailment. As has happened so often in the history of medicine, all of the king's physicians—including the knowledgeable monarch himself—had viewed each of his many symptoms as a separate entity, an opinion that contributed neither to the cure nor even to the alleviation of the king's lifelong suffering.

Dr Selle had modestly entitled his publication about his royal patient a "Case History of the last blessed King of Prussia, Frederick the Second, Majesty," and confined himself to medical observations. So far as the title and most of the contents are concerned, Selle had presented an impersonal case history. Throughout this description of the king's illness we find evidence of Selle's profound admiration for the personality of his illustrious patient. To quote one of the initial paragraphs:

> The constitution of the King was so powerful and his medical conduct so simple that one could observe the very movements of nature as it resisted a severe illness for a considerable period of time under the most unpropitious circumstances. It was therefore possible to distinguish the changes actually brought about by the use of medication. In this respect is it possible for the physician to derive instruction from the natural and unimpeded course of an illness?

Selle's subsequent summary of Frederick the Great's symptoms reveal in their totality the actual nature of a disease, which during his lifetime was as yet unknown and therefore not treatable as a whole. In Selle's matter-of-fact description we read that even in his early years the king had suffered from a significant weakness and sensitivity of his stomach, so that he frequently vomited all he had eaten. In his later life, although he ate voraciously and digested well, he continued to suffer from so irritable a digestive tract that he had to be purged repeatedly, although he was also subject to attacks of spontaneous diarrhea.

In addition to that the king was beset at an early age by recurrent attacks of gout and hemorrhoids; and as the former—gout—became regular, and led to chronic pain, the physicians attempted to cure it by treating the hemorrhoids with venesection and mild purges. At the age of 36 the king suffered a transitory attack of hemiplegia which underwent a spontaneous remission and never recurred. This much Dr Selle found out from interviews of court personnel; only at the age of 75 did the king feel inclined to inform his doctor of the details of his medical history. It was at a time when he was feeling relatively well and when he suffered only from occasional and transitory weakness and colics, which he attributed to his hemorrhoids but which were mostly caused by the wear and tear of old age and his greatly weakened power of digestion. So much we gather from Dr Selle's tactful and professional case history.

Dr Johann Georg Zimmerman

How different was the story published by his successor, the famous Dr Zimmermann, which makes the doctor part of the title and obtrudes his personality upon the attention of the reader: *Doctor Zimmermann's Conversations with the late King of Prussia*.[4]

Just as no man is a hero to his valet, few men are heroes to their personal physician, especially when the physician concentrates all his skill and attention upon his one patient as is the case with the court doctor, who gets to know his patient in his somatic configuration and intimate habits as well as in his social and psychological make-up. In ordinary life and among ordinary people, a physician may tell his patient to maintain a certain diet, to stop smoking, to control his alcohol intake and to take his medication according to schedule. All the doctor can do is to hope that the patient will follow his orders. A personal physician and a court physician is present whenever the patient follows or transgresses his orders. He is present in those many

moments when his charge ceases to be a patient and conducts himself as any man, with ideas that bear no relation to his illness; and frequently they may be of so private a nature that the doctor should not even—as the Chinese suggested—"share them with his wife." But the temptation to acquire vicarious status by knowing so much about the private thoughts and oddities of behavior of as illustrious a patient as Frederick the Great, so irresistibly dazzled Zimmermann as to tell it all in his letters to various friends. These friends saw no reason not to enhance their own status by withholding these invaluable bits of intimate information about the great king and published them without Zimmermann's permission as *Fragments about Frederick the Great.* This publication placed Zimmermann in the embarrassing position of having to deny the correspondence altogether, or of making the best of his indiscretion by publishing the contents of his letters in his book about his conversations with the dying king. Obviously the subsequent publication that was much criticized was based on a diary that Zimmermann kept during his stay at the Prussian court.

By way of contrast to the publication of Dr Selle I wish to cite a few passages from *Doctor Zimmermann's Conversations with the late King of Prussia,* which he had admittedly spiced with "several curious particulars and anecdotes of that extraordinary prince."

Naturally, the information of Selle's notes and a multitude of court personnel was available to Zimmermann who did not refrain in his book from expressing his mild amusement at the foibles of his illustrious patient. Where Selle had simply stated that King Frederick had always eaten large quantities of food, Zimmermann felt it incumbent upon himself to detail the somewhat ludicrous eating spree upon which the king had embarked during his physician's temporary absence:

> At three in the afternoon I found the king in the most painful situation; everything was changed and become worse. When in good humour, he had taken his medicine of dandelion and drank coffee; after this, he had applied from half after three in the morning till seven, to public business. Great part of the morning he had spent in eating, for as soon as I left him, a plate of sweetmeats, composed of sugar, whites of eggs, and cream, that had been brought him, one of which I ate, and found the cream very sour. His majesty ate the whole plateful for his breakfast; and afterwards, strawberries, cherries, and cold meat. At eleven his servants found great difficulty in getting him on horseback. He remained there three hours, in the great garden of Sans Souci, galloped almost the whole time, and returned very much weakened and exhausted. When he sat down to table he had no appetite; and immediately after dinner he was seized with a vomiting.
>
> At three o'clock of the next day the king was again attacked by a colic, the consequence of indigestion; and he was in very bad humour. At dinner he had eaten plentifully of fresh eels. . . I have reflected a good deal upon what you said yesterday, respecting the dropsy, which from your hints I have reason to apprehend. I am now convinced you are right; for I pressed my legs with my finger, and the part remained hollow. This is an evident symptom of the dropsy.

Zimmermann's book contains many convincing references to the king's own medical acumen which often made him a partner in treatment rather than a mere patient. Initially the king denied that he was suffering from dropsy although he actually was sufficiently conversant with that affliction to recognize it when it could no longer be denied. Thus, later, he observed:

Although the king's observation was absolutely correct in describing pitting edema, Zimmermann tried to comfort him by assuaging the fear caused by that symptom. Frederick, however, was convinced of the sad state of his health and replied: "O! do not speak to me of hopes!"

Dropsy and ascites were actually symptoms of one devastating disease from which the king had suffered since he was a youth: the symptoms included generalized and ever-worsening ascites, gastric colics, violent sweating, severe headaches and accelerated pulse; he furthermore suffered from painful limbs, and dark red urine. It is this last-named symptom that confirms the clue that was suggested by Hunter and Macalpine's brilliant study, *George III and the Mad-Business.*[5] In their totality, the symptoms obviously prove that Frederick the Great, like his blood relative George III, was a sufferer from porphyria.

Unlike Selle who confined his case history to medical observations, Zimmermann also published his nonmedical conversations with the king and included his patient's political views. It is here that he leaves the strict confines of medical reporting, and exposes himself to sharp criticism. In fact, leading personalities, even a century later, have called him vain and self-serving, and the well-known Berlin physician Ernst Ludwig Heim spoke of him as a "fool and an egotist."[6]

Lord Moran

The keeping of a diary must be an enormous temptation for physicians to highly placed personalities. This becomes evident from the hotly debated book on Winston Churchill[7] which was derived from the diary notes of his personal physician, Lord Moran.

Needless to say, both publications, that by Zimmermann and by Lord Moran, would seem to be in contradiction to the earliest Greek and Chinese injunctions about privileged communication. But, beyond this, both publications have much in common: both describe patients who were of extraordinary stature, highly placed in public and political life, subject to hostility as well as to fanatic devotion. Both Frederick the Great and Churchill had considerable medical knowledge, at least so far as their own persons were concerned, both wanted to be consulted about their treatment and followed it only if they were convinced of its rationale. Both men, furthermore, had outstanding personal foibles, even in their bedroom attire, which their physicians did not forget to detail. Frederick the Great, even in bed wore his large tricornered hat which he politely doffed upon his physician's entrance; his other garments were ill kept and spotted by snuff. In contrast to the formal behavior but shabby and unkempt appearance of the king, Churchill is pictured by his physician

as having been extremely uninhibited in the presence of his doctor. He made elaborate preparations for bed, wearing a silken shirt, and using various creams for his face and bald head, and dosing himself with sleeping tablets at night and pep pills in the morning. Unlike Dr Zimmermann, Lord Moran served as general friend, confidant and sounding board to the Prime Minister, and we learn from his book that for several years England's fate was guided by an ailing man who had to persuade himself with the utmost energy that he was fit to do his job and that his continued service would be for the good of his country.

Zimmermann attended the king for less than a year, not long enough to develop even a trace of the personal affection and devotion that are so evident in Lord Moran's diary notes about his patient. But, in spite of this admiration and devotion in Lord Moran's 25 years of service to the great man, there is, as the anonymous (but apparently English) reviewer in *The New York Times* book review (*The New York Times,* May 13, 1966) stated, "something morbid about publishing so clinical a record of a great man; possibly something 'unethical' as Americans put it."

Dr Max Schur

Needless to say, these two books—that by Dr Zimmermann about the last years and final illness of King Frederick the Great and that by Lord Moran about Churchill—do not exhaust the diary literature of physicians about their famous patients. A third such volume that should be included in this study and that has recently been much discussed is the book by Dr Max Schur entitled: *Sigmund Freud: Living and Dying.*[8] Again, we have the publication of a painfully detailed case history of a great and famous man, Sigmund Freud, who suffered for nearly 20 years from cardiovascular difficulties and from the ravages of a carcinoma of the jaw. The author, Dr Max Schur, had been psychoanalyzed and, in addition to his practice of internal medicine, was a practitioner of psychoanalysis. This, he seemed to have thought, entitled him to psychoanalyze Sigmund Freud's behavior as a patient; and to tell the world not once, but repeatedly, and ad nauseam, of Freud's "nicotine addiction," that made it impossible for him to forgo his beloved cigars which aggravated both his cardiovascular difficulties and the carcinomatous condition of the lower jaw. To be sure, Schur's book appeared long after Freud had succumbed to the ravages of his illness. But again, I wish to remind the medical reader that the Hippocratic oath, as well as the Chinese injunction, impose *complete discretion* upon the physician, and use the word *never* to speak of what is experienced in the patient's house.

Dr Janet Travell

There is one other book that seems to be indispensable in this discussion: *Office Hours Night and Day.*[9] It deals with medical practice within the White House and was written by Dr Janet Travell, who was John F. Kennedy's personal physician when he was still a senator and later became physician to the White House. Unlike the other, earlier-mentioned books, Dr Travell's volume refrains from the use of any condescending or patronizing tone towards her late patient. But it confirms a diagnosis that was made by thousands of physicians, simply on the basis of President Kennedy's appearances on the television screen. The author, Dr Travell, confirmed the fact that President Kennedy's frequently swollen face was induced by medication; that he suffered from Addison's disease, and was given regular doses of cortisone, perhaps in all too liberal quantities, and hence not only had the typically stuffed-up facial contour, now known as "moon face" or "cushingoid," but he also may have lived and often acted under the stress of cortisone medication, which was prescribed for him to counteract his adrenal insufficiency.

In the literal interpretation of all existing codes of ethics—even including that of the American Medical Association—none of these books, about the health of Frederick the Great, Churchill, Freud and Kennedy, should ever have been published. Indeed, we all may have our thoughts about ethics and the inviolability of privileged communication but, as medical historians, we must welcome as treasures these publications as the purest source material that may ever become available to us.

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Medical Schools of the West

The University of Southern California School of Medicine

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Founded as the second school of the University of Southern California (USC) in 1885 by Joseph Pomeroy Widney, MD, the School of Medicine survives today as one of three private coeducational medical schools in the state of California. Its beginnings were as fragile as those of many other California schools: Dr Widney and ten colleagues rented the Vache Freres Winery, a two-story brick building at 445 Aliso Street in Los Angeles (Figure 1), as the first teaching quarters of the medical school.[1] Dr Widney believed strongly that the medical students should be well prepared in Greek and in Latin and personally screened the applicants. He consulted with Harvard University and the University of Pennsylvania for appropriate curricula, set the tuition and printed the schedules and curricula. The first bulletin states that graduates must be 21 years of age and of good moral character, have completed three years of the study of medicine, passed the examinations, dissected an entire cadaver and paid the fees, which amounted to $315 for three years. Dr Widney's first catalogue also stated that "good boarding with room rent can be had in the city for from $5 to $10 a week." After the first year, he bought the winery and the medical school remained in this location for ten years. The first class was graduated in 1888 and consisted of eight men and one woman.

During the ten years on Aliso Street, there were many changes in faculty and in curriculum. The three-year course was changed to four years and attendance was made compulsory. Unable to afford to build or buy a teaching hospital, the clinical teaching sites became the Los Angeles County Hospital and the then brand-new California Hospital. In 1909 the school affiliated with the University of California as the Los Angeles Medical Department of the University of California and offered undergraduate courses until 1914. Students who were in school during the years of the changeover were permitted to choose their alma mater, and thus the inscription on their diploma; many of them felt an allegiance to USC and considered themselves alumni. The actual sequence of events after 1914, as related by Viola Lockhart Warren[2] in her article "The Old College of Medicine," is complicated. However, the University of Southern California promptly affiliated with the College of Physicians and Surgeons, which became USC School of Medicine.

The School of Medicine was closed from 1920 to 1928; it has been graduating physicians each year since it reopened. During World War II, classes were accelerated even though many of the male faculty members accepted assignments in overseas military units.

Throughout its long history, the institution has trained physicians for the practice of medicine in California and it is estimated that of the more than 2,800 living alumni, approximately three fourths practice within 100 miles of Los Angeles. Through its affiliations with community and public general hospitals, its patient care, teaching and research activities have enhanced the health of the area's citizens while providing superb training facilities for young physicians.

Organization of the School of Medicine

The medical school is organized by basic science and clinical departments under the direction of Dean Allen W. Mathies, Jr, MD. There are 764 full-time, 63 part-time and 2,582 voluntary faculty members. This diverse faculty instruct 581 medical students in a four-year degree granting program leading to the MD degree. The faculty also instruct some 85 graduate students enrolled in PhD degree granting programs; 1,000 interns, residents and fellows enrolled as postdoctoral associates in graduate medical education training programs, and 4,000 health-related trainees in more than 100 preparatory programs (nurse midwives, physician's assistants,

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nurse practitioners, medical technicians). More than 9,000 physicians and nurses enrolled in continuing education programs directed by the Division of Postgraduate Education in 1980-1981.

Students and Their Curriculum

USC School of Medicine admits 136 entering students each year. These students are chosen by members of the admissions committee from an applicant pool of approximately 4,000; about 1,000 of the applicants are personally interviewed. In the 1981-1982 entering class, the grade point average was 3.59. A total of 118 students held baccalaureate degrees, 12 master's degrees, and six PhD degrees. There were 4 second-year and 16 third-year transfer students admitted. The total student body is 581 (435 men and 146 women); of these students 138 are US citizens designated as ethnic minorities.

The curriculum is organ-system oriented. Students learn about normal human functioning during the first year with the basic sciences centered on anatomy, biochemistry, physiology and human behavior. During the second year the emphasis is on the pathologic condition of patients with the basic sciences centered on pharmacology, pathology and microbiology. Small groups of five students assigned to one physician meet one to two half-days each week in Introduction to Clinical Medicine. In these groups students study growth and development, history taking and physical examinations, as well as learn about community settings—for example, how patients are cared for in alcohol rehabilitation centers, nursing homes and retirement homes. They learn how to communicate with patients and how to handle the frustrations of pain and suffering and death and dying.

In the final two years of medical school, a fully rotating two-year continuum permits the students flexibility in scheduling a combination of required and selective clinical clerkships with the permission of a faculty adviser. An increased number of clinical clerkships are taught in the affiliated community hospitals of the School of Medicine. From 60 to 70 graduating students choose to take their first postgraduate year of training in one of USC's affiliated hospitals, which is not surprising given the large ratio of California citizens who choose this school. Nearly all of USC's medical school graduates continue specialty training leading to board certification.

Affiliated Hospitals of USC School of Medicine

For many years the primary teaching affiliate of the School of Medicine has been the big public general hospital, now known as the Los Angeles County-USC Medical Center (Figure 2). Major changes began to take place in the relationship with the County of Los Angeles in the 1960s. As Loma Linda School of Medicine moved to its new home in Loma Linda, California, and the California College of Medicine became University of California, Irvine, USC took over all of the professional services of the huge hospital, not without some trepidation. That trepidation was shared by the accrediting agency that returned to review the school's progress just three years later. The transition was very successful. Assuming the professional responsibility with full-time faculty, the voluntary faculty continued to be supportive and to this day shares the patient care and teaching load. Located on a 98-acre site, the big medical center has been called the "largest teaching hospital in the world." Today, the number of licensed beds has been reduced from more than 3,000 in the early 1960s to 2,105 and the budgeted patient census is approximately 1,500, a tribute to the research procedures which have reduced inpatient admissions.

Today the Los Angeles County-USC Medical Center

Figure 1.—A painting showing the building that was the first home of USC School of Medicine. The school's founder, Dr Joseph Pomeroy Widney, leased the two-story building on Aliso Street in Los Angeles in 1885.

is more than 100 years old; one in every 225 persons born in the United States is born at Womens Hospital where the large obstetrics and gynecology service is rated one of the best in the nation. The service delivered its first "test tube baby" in May 1982; to date, three healthy "test tube babies" have been successfully delivered there. Near the obstetrical service is a fine neonatology service. Major research projects include reproductive biology, fetal monitoring and high-risk pregnancies.

The 18-story General Hospital directs acute medical and surgical care programs, critical care, coronary care, kidney dialysis and transplant, and oncology. The Department of Emergency Medicine controls a large emergency training and patient care system. At the Pediatric Pavilion, care is provided for sick children, but also for adults admitted with undetermined infectious or communicable diseases. The Psychiatric Hospital functions at maximum capacity at all times. The Medical Center provides 24-hour per day care, 365 days per year, with board-certified physicians who are members of the USC School of Medicine faculty.

Other major affiliates of the School of Medicine are the following: Childrens Hospital of Los Angeles, a regional pediatric hospital; The Hospital of the Good Samaritan, where much of the school's private practice consultation work is carried out; Orthopaedic Hospital, which is the location of the Department of Orthopaedics and a large research laboratory in bone mechanics; Presbyterian Intercommunity Hospital, which is the site for the family medicine residency training program, and Huntington Memorial Hospital. The Doheny Eye Foundation is located on the Health Sciences Campus and is the home base for the Department of Ophthalmology. Rancho Los Amigos, a large categorical care rehabilitation hospital, houses patients with chronic disabilities, primarily those disabled with traumatic injury. Major rehabilitation programs are the subject of research and development to enable those persons disabled through disease and injury to be productive. The only acute service still maintained at this facility is the well-known Liver Service; due to recent funding cutbacks within the County of Los Angeles, other acute care programs have been discontinued at this site. The University's physical and occupational therapy degree granting programs, research and teaching programs in gerontology,

Figure 2.—A view of the Health Sciences Campus with the upper story of General Hospital, Los Angeles County-USC Medical Center in the distant background (center).

and strong neurological, orthopedic and cardiac rehabilitation programs are located on the Rancho campus.

The School of Medicine is a newcomer to the private practice of medicine but in the last year The Richard Thomas Barton Diagnostic Clinic has opened; physicians in the community may utilize USC School of Medicine faculty as a resource for consultation and second opinions. Just completed is the Kenneth Norris Jr Cancer Research Institute, a $38,000,000 facility with 60 inpatient beds and a large outpatient facility, which serves as the heart of the USC Comprehensive Cancer Center program (Figure 3). The Center, designated in 1970, offers programs in basic and clinical research, patient care, epidemiology and community education. The Cancer Hotline is one of the busiest in the nation.

Research and the School of Medicine

The School of Medicine is active in a broad area of research efforts. Direct funding in the past year has exceeded $22,000,000, which placed USC as one of the top 20 schools in the nation in ability to attract peer review awarded National Institutes of Health funds. More than 200 funded projects are actively directed by research scientists of national and international stature at the present time. Short-term research training for USC medical students is funded by a federal grant.

Conclusion

In 1981 the Liaison Committee on Medical Education of the AAMC/AMA found USC School of Medicine in good health and, following a self-study and a site visit, renewed the school's accreditation for ten years. Thus, our 100th birthday will find us in good health and in good spirits with a continuing will to prepare practicing physicians for the Southern California region.

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Figure 3.—The USC Comprehensive Cancer Center is housed in the new Kenneth J. Norris Jr Cancer Research Institute on the Health Sciences Campus. The 150,000 square foot, nine-story building has 30,000 square feet of laboratory space, advanced radiation therapy and diagnostic equipment, beds for 60 patients who can benefit from treatments under study and facilities for 100 outpatients a day.

Hepatitis Among Hospital Employees

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The risk of acquiring hepatitis associated with work in a moderate-sized acute-care teaching hospital was determined by a seroepidemiologic survey of hepatitis B surface antigen and antibody. A blood specimen and a completed questionnaire were obtained from 76 percent of the staff members involved in patient care activities and all preemployment applicants (a total of 767 persons).

One employee was found to have transiently positive tests for hepatitis B surface antigen, whereas 94 (12.2 percent) were found to have hepatitis B surface antibodies. Using the national incidence rate for volunteer blood donors of 4.4 percent as a norm, significantly higher antibody incidence was seen in nursing personnel (16.9 percent), laboratory workers (14.0 percent), surgeons (37.5 percent) and dental workers (40.0 percent). Rates were not significantly raised among house officers, internists, respiratory therapists or housekeeping employees. Increased incidence was statistically related to age and known history of hepatitis, but not to sex, known needle-stick exposure, contact with patients having hepatitis, prior blood transfusion, blood handling or nonhospital exposure to hepatitis. In persons whose tests were positive for antibodies there was a 4 percent increment per decade of age among long-term employees; duration of employment approached significance as a risk factor. Of those with hepatitis B antibody, only 16 percent were aware of a prior bout of hepatitis.

Hepatitis B is among the most common infectious risks of hospital employment,[1] occasioned by contact with patients. Serologic evidence of prior infection among health care workers is two to ten times higher than in the population at large.[2-4] Illness or asymptomatic transmission may occur in hospital staff after caring for patients (or handling their blood or secretions) with either active hepatitis or subclinical disease.[5] Hepatitis has also been transmitted, albeit infrequently, from health workers to patients, with outbreaks traced to dentists, oral surgeons and, in isolated episodes, from a general practitioner, a gynecologist, a nurse and a respiratory therapist.[6-11] Infection may be acquired through close personal contact,[1,9,11] but more commonly occurs following percutaneous inoculation of blood.[12]

Prior studies of hepatitis risk among US hospital health care workers have been somewhat specialized in scope. Serologic surveys have reviewed employees of two large metropolitan hospitals serving predominantly indigent patients[13,14]; prevalence among employees in the National Institutes of Health Clinical Research Center[4]; hospital personnel in two West German hospitals,[3,15] and the staff of an Australian hospital where exceptionally high patient hepatitis rates were found.[2] The occurrence of acute hepatitis has also been monitored among such specialized health care personnel as those employed in mental institutions[16] or a tertiary care hospital.[5] In addition, several studies have surveyed physicians in general[17-19] and specific occupations, including hemodialysis workers,[20] adult and pediatric oncology staff,[21,22] surgeons[23] and laboratory workers.[24]

We wished to clarify the hepatitis risk within a Veterans Administration (VA) Hospital because no review exists for this system. Additionally, few studies of hepatitis antibody prevalence address moderate-sized acute-care hospitals serving a population with low hepatitis incidence. Our further purpose was to determine the influence of other variables such as age, total duration of health care employment, specific occupation, blood handling, known prior contact with hepatitis pa-

Refer to: Palmer DL, Barash M, King R, et al: Hepatitis among hospital employees. West J Med 1983 Apr; 138:519-523.
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tients, known needle-stick exposure and prior awareness of clinical hepatitis.

Background

The Albuquerque VA Hospital is a 400-bed acute-care hospital with 1,100 employees, about 800 of whom are involved directly in patient care. Ethnic background among patient-care employees is 60 percent white non-Hispanic, 33 percent white Hispanic, 5 percent black and 2 percent other (0.2 percent Asian). Most physician patient care is provided by supervised house staff in continuous rotation among several hospitals. The hospital serves as a referral center for cardiac catheterization, open-heart surgical procedures, hemodialysis and renal transplantation. General medical, surgical and psychiatric inpatient and outpatient services are provided as well as special services in surgical and medical intensive care, coronary care, home and center dialysis, oncology and respiratory care. About 15 to 20 open-heart cardiac surgery patients are operated on each month and 15 patients a month receive blood or plasma for oncologic or hemorrhagic diseases.

Hepatitis B is relatively common in the Albuquerque community, related to known parenteral drug abuse. In the VA Hospital, however, only five to ten patients with newly detected hepatitis B have been treated per year, a rate of 5.5 to 11.0 per 10,000 admissions. In addition, one to five patients receive long-term care in the hepatitis B-positive section of the hemodialysis unit. About 20 to 25 hospital employees a year receive hepatitis B immune globulin because of known exposure.

Materials and Methods

In the 18-month period between June 1979 and November 1980, all employees with patient-care duties and job applicants were requested to participate in an investigation of hepatitis. Employees had blood drawn and were given a questionnaire to determine age, occupation, duration of employment, hospital location of employment, prior history of hepatitis, hepatitis in their family, frequency of blood handling, occurrence of known needle-stick exposure and history of blood transfusions. Subjects having had prophylactic inoculations of hepatitis B immune globulin or immune γ-globulin for needle or mucosal exposure in the past two months were excluded. Tests for hepatitis B surface antigen and antibody were done by radioimmunoassays (Ausria II and Ausab kits, Abbott Laboratories, North Chicago, Ill).

Data obtained were compared with baseline values from a national serologic survey of incidence of hepatitis B surface antigen and antibody among first-time volunteer blood donors in 14 cities in the United States.[25] Data were analyzed for significance using the x^2 test or direct (binomial) probability where applicable.

Results

A blood specimen and a questionnaire response were obtained from 767 of the 848 employees (90.4 percent)

TABLE 1.—*Serologic Evidence of Hepatitis (Hepatitis B Surface Antibody) Related to Health-Care Occupation Compared With National Blood Donor Rates**

Category	Total Tested N=589	Positive for Antibody Number (Percent) N=80 (13.6)	Level of Significance
Physicians	181	15 (8.3)	NS
Medical	28	3 (10.7)	NS
Surgical	8	3 (37.5)	<.01
Pathology	5	1 (20.0)	NS
House officers	140	8 (5.7)	NS
Dentists	5	2 (40.0)	<.05
Dental assistants	8	1 (12.5)	NS
Laboratory workers	50	7 (14.0)	<.01
Radiology	23	3 (13.0)	NS
Nursing	307	52 (16.9)	<.001
Supervisors	8	3 (37.5)	<.01
Operating room	23	6 (26.1)	<.001
Wards	209	32 (15.3)	<.001
Intensive care units	54	7 (13.0)	<.01
Dialysis	13	4 (30.8)	<.01
Building management and engineering	15	0 (0.0)	NS

NS = not significant

*National volunteer blood donor incidence rates of 4.4 percent[25] were used for comparison; statistical analysis by direct (binomial) probability, using a one-tailed test.

determined to be involved directly in health care activities. Among the nonphysicians (see below) those not volunteering for testing were equally distributed by sex and occupation. Only one person was found to have hepatitis B surface antigen. He was unaware of illness and subsequently converted to a positive-antibody state without sequelae. For simplicity of analysis, this person was thereafter considered in the same category as those 94 employees found to have hepatitis B antibodies. This resulted in an antibody incidence among all employees tested of 12.6 percent. Nearly all of the nursing staff, including nurses at higher administrative levels, volunteered for the study. Staff physicians were among the most difficult to enlist in the study; only 75 percent volunteered for sampling, possibly due to anxiety about employment changes dictated by possible hepatitis antigen carriage.

Table 1 shows the data concerning rates by category of employment. Compared with the national baseline of 4.4 percent,[25] a significant increase in prevalence was detected among nursing personnel, laboratory workers, surgeons and dentists. Among all physicians, however, only surgeons had a statistically significant ($P<.01$) increased prevalence, though fulltime medical and pathology staff showed a 10 percent and a 20 percent rate, respectively. The rate of 5.7 percent of antibody-positive findings among house officers was close to the national incidence figure for volunteer blood donors. The rate for laboratory workers was significantly above the national comparative standard, but there were no differences among the various types of laboratory workers (for example, microbiology versus hematology versus chemistry sections). Internal check showed frequent job transfer and night-time cross coverage in the laboratory and a uniformly high rate of blood handling.

Nursing personnel of all categories showed significantly raised rates, with the highest (37.5 percent) among supervisors, apparently related to age and duration of occupation. On the other hand, the rates for operating room nurses and dialysis nurses were also significantly higher (26 percent and 31 percent) than the average of all nurses (17 percent), reflecting specific occupational risk. Nurses on surgical and medical intensive care units had no higher prevalence of antibody than general nurses, presumably because of high turnover rates among these units (average stay two to three years). Sampling from preemployment applicants showed a hepatitis B antibody rate of 8.1 percent. Although significantly higher than the national volunteer blood donor rate, most of these potential employees had already been in health care occupations before applying for this job.

Table 2 shows the incidence of hepatitis antibody related to demographic factors of sex, age and duration of employment. Although there were no differences between male and female employees, the age-related differences were significant at the $P<.01$ level. The incidence of hepatitis antibody as related to increased length of employment approaches, but does not reach, statistical significance ($P<.10>.05$). In retrospect, this question was probably not understood as intended, that is, to elicit information on duration of employment at the current ward assignment, rather than total health care employment. Of the other risk factors considered in our questionnaire (Table 3), only the history of hepatitis was significantly related to antibody state, with 16 percent of antibody-positive employees having a history of hepatitis as opposed to a prior hepatitis disease rate of 5 percent of those who did not have antibodies ($P<.001$). A history of blood transfusions, known needle-stick accidents, handling of blood and known (family) hepatitis exposure was not statistically significant relative to positive-antibody status. More than 90 percent of all hospital employees in this survey consider themselves frequent handlers of blood, decreasing the chance that this response would detect differences. Of the 35 employees with a personal history of hepatitis, several undoubtedly did not have hepatitis B, as 22 did not have antibodies to hepatitis B. Of the 13 with a history of hepatitis six had the illness before entering the health care field. Furthermore, by this survey, 84 percent of those who had detectable antibody had no prior knowledge of hepatitis.

TABLE 2.—*Incidence of Hepatitis B Surface Antigens or Antibodies Among Hospital Employees in Relation to Sex, Age and Duration of Employment*

Category	Number of Employees*	Number Positive	Percent Positive	Level of Significance
Sex†				NS
Male	381	48	12.6	
Female	380	41	10.8	
Age				$P<.01$
20	1	0	0.0	
20-29	158	13	8.2	
30-39	217	21	9.7	
40-49	187	25	13.4	
50 and over	128	27	21.1	
Duration of employment years				$P<.10>.50$
0-9	292	43	14.7	
10-19	88	18	20.5	
20-29	36	2	5.6	
30 and over	13	1	7.7	

NS = not significant

*Totals are not identical due to omission of response on some questions.
†Totals (sex only) include employment applicants as well as current employees.

TABLE 3.—*Hepatitis Exposure by Questionnaire as Related to Hepatitis B Antibody State*

Question	Positive response on questionnaire over total response (percent)*		
	Positive for Hepatitis B Antibody	Negative for Hepatitis B Antibody	Level of Significance
History of hepatitis?	13/79(16.5)	22/411(5.4)	$P<.001$
Previous blood transfusions?	13/95(13.7)	43/368(11.7)	NS
Needle-stick accident?	38/66(57.6)	214/340(62.9)	NS
Handle blood during work?	57/66(86.4)	310/337(92.0)	NS
Hepatitis in family?	9/76(11.8)	51/484(10.5)	NS

*Totals are not identical due to omission of response on some questionnaires. Includes only current employees.

Discussion

This study was undertaken to determine the occupational hazard of hepatitis among hospital employees in a medium-sized, university-affiliated, acute-care hospital serving a population of relatively low disease incidence. Because acute hepatitis may be underreported in subclinical or inapparent cases by up to tenfold,[4,13] risk associated with employment was assessed by seroepidemiologic detection of both antigen and antibody. The incidence of hepatitis antibody among all employees was 12.6 percent and, while slightly lower than that in some surveys,[3] was generally in the range seen in other United States facilities[4,13,14,23] for house staff, surgeons, medical technologists, dentists and nurses.

The 5 to 15 new cases of hepatitis seen in this hospital per year undoubtedly underrepresents the risk to health care workers because many patients with known antigenemia return repeatedly for continued care. This group includes patients receiving renal dialysis and those with chronic hepatitis or who are positive hepatitis B surface antigen carriers who do not have hepatitis. In addition, studies for hepatitis B surface antigen among consecutive adult inpatients would indicate that as many as 83 percent of patients with hepatitis B have mild hepatitis but are not known carriers or detected by routine studies conducted during stay in hospital.[1]

The incidence of seropositive findings was particularly high among surgeons (37 percent), dentists (40 percent), laboratory technologists (14 percent) and nursing personnel (17 percent). These results are in accordance with those found by others. Although the overall rate of 8.3 percent among physicians is about

twice the national rate for volunteer blood donors (4.4 percent), it is significantly below the physician rate reported in Germany and England, except for the surgeons among this group.[3,15,18,23] Surveys of physicians at medical meetings in 1975 and 1976 have shown incidence rates of 18.5 percent[17]; these higher rates may in part result from the self-selection of those particularly concerned because of known exposure. The low rate among house staff (5.7 percent) in our survey undoubtedly reflected their shorter job tenure and younger age and is consistent with the observation of frequent seroconversion during training.[17,25] Among nursing personnel, the highest rates were found in supervisory nurses, dialysis staff and operating room nurses, attesting to the risks incurred during long employment in nursing on the one hand and the higher risks during surgical and dialysis procedures on the other. Although nurses in both medical and surgical intensive care units were significantly more likely to have the antibody than nonmedical workers, their rate was not higher than other nurses' despite known hepatitis risks of this occupation.[11,15] This unexpected finding may in part be due to the very high turnover among personnel in intensive care units. Among nursing personnel in particular, there is a high rate of change from one nursing unit to another within the hospital leading to a methodologic problem in attributing risk.

Hospital areas with high risk of occupational exposure included surgery (both operating room nurses and surgeons), laboratory (including pathologists) and hemodialysis. These areas have been cited frequently for risks primarily caused by accidental inoculation or splash-exposure to antigen-positive blood.[1,4,12,13,20,24,26] Unlike previous studies in West Germany,[3] occupation in building management (cleaning services) did not increase the apparent chance of acquiring hepatitis. Age was very significantly associated with the risk of having the antibody in this survey (see Table 2). Thus, 8 percent of all employees in the 20- to 29-year-old range were antibody-positive, whereas those aged 50 years or older had a 21 percent rate, a nearly linear 4 percent increase per decade. A limited recheck of older persons with positive titers indicated that almost all had been employed for their entire adult lives in hospital-related health care. Duration of employment appears to be related to risk of incurring hepatitis; the 4 percent increment per decade most likely reflects hospital contact rather than hepatitis B being incurred in the community.[25]

Although 31 percent of physicians in other studies[17] have indicated that they recalled earlier hepatitis, we found only 10 percent among physicians in this survey. Similarly, only 16.5 percent of all hospital workers in whom antibodies were detected could recall a history of hepatitis. Because 5.4 percent of those who had negative antibody titers had a similar history, at least a third of such histories would appear to be due to hepatitis non-B disease. This would indicate an apparent to inapparent hepatitis B infection ratio of about 10:1. Furthermore, personnel who had antibodies generally were not aware of a critical incident (needle-stick or mucosal exposure) involving a patient with hepatitis. Thus, much of the risk incurred by hospital employment comes from work with patients (or specimens) not recognized as having hepatitis and results in asymptomatic seroconversion.

The rate of antigenemia seen in this study (0.1 percent) was surprisingly low in view of the active dialysis unit—which contains patients who have active hepatitis in a segregated section—and an active oncology unit. Rates of about 1 percent have been found in other surveys of hospital personnel.[2-5] Possible reasons for the low rate of hepatitis B surface antigen among employees include use for the past four years of hepatitis B immune globulin following mucosal splash or needle-stick exposure to antigen-positive blood. During this interval, about 20 to 25 episodes per year of known exposure (predominantly via needle-stick and often involving several persons exposed to the same patient) have required treatment with hepatitis B immune globulin. Among the employees given hepatitis B immune globulin, there have been no known subsequent cases of hepatitis in the past four years, in line with the reduction found in the VA collaborative study.[12] For the past seven years, patients in the hemodialysis unit who have hepatitis B surface antigenemia have been segregated and, whenever possible, cared for by personnel known to have antibodies.[20,27]

With the development of an effective hepatitis B vaccine, the importance of detecting high-risk occupations and sites within a hospital increases. Although infrequent, the transmission from medical staff to patients is also now well documented.[6-11] Early studies clearly indicate both the immunologic potency of the hepatitis vaccine[28] and its efficacy in protecting dialysis personnel and patients.[29] In a hospital similar to ours, vaccine would be used extensively for high-risk groups, with priority for distribution going first to surgeons, dental staff, operating room nurses and dialysis workers. In the next priority category would be laboratory technicians, intensive care unit nurses and all other nurses, with the last priority being all other physicians, including nonsurgical house officers. On a cost-effectiveness basis, vaccine should only be given after determination that the titers of these high-risk staff are antibody-negative. This is based on a current price of about $100 per course of vaccine per employee, an incidence rate of 12 percent for current employees, and an estimated $8.00 for hepatitis B surface antibody per test. Thus, excluding 12 antibody-positive employees per 100 would save $1,200 of vaccine costs at less than $800 hepatitis B antibody test costs. The expense of such a vaccination program may in part be defrayed by the reduction in use of hepatitis B immune globulin; in our hospital 18 of 26 employees given hepatitis B immune globulin in the past year were in high-risk categories. Vaccine cost must also be prorated over the lifetime of its protection (at least five years).[30] Coupled with reduced hepatitis B surface antigen testing after exposure, vaccine use thus approaches the cost of current pro-

tective measures for hepatitis-exposed hospital personnel.

In summary, we have shown that for a medium-sized teaching hospital with a primary and tertiary mix and house staff and nursing teaching functions, the risks of incurring hepatitis are strongly related to age (and probably duration of hospital employment) with an increment of about 4 percent per decade of work in the health-related field. Most risk appears to come from unrecognized cases of hepatitis without known needlestick exposure and 83 percent of the hepatitis that occurs among employees (as detected by antibody state) is asymptomatic or unrecognized. Service areas of highest risk include dialysis units, operating room, laboratories and dental units, with a probable increased risk in intensive care units. Physicians and nurses at highest risk include surgeons, pathologists, operating room nurses and dialysis nurses. Low (or normal) rates were found among medical staff physicians, cleaning personnel and house officers.

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Maternal Serum α-Fetoprotein Screening for the Detection of Neural Tube Defects

Report of a Pilot Program

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We tested 10,715 low-risk pregnancies in a voluntary maternal serum α-fetoprotein screening program for the detection of neural tube defects in California. In all, 5.3 percent of women had one elevated serum level, 3.3 percent were referred for sonography and 1.5 percent for amniocentesis. There were 12 cases of open neural tube defects (1.1 per 1,000); all of the mothers had one elevated serum α-fetoprotein level: nine (75 percent) completed the protocol and the neural tube defects were correctly identified. No normal pregnancies were terminated. The risk of an open neural tube defect occurring was about 1 in 50 after the first abnormal serum level and 1 in 15 at amniocentesis. We found a significantly increased risk for fetal death and low birth weight after one elevated serum α-fetoprotein level, though the likelihood of a normal pregnancy outcome was about 80 percent. Maternal serum screening was also useful in identifying twin pregnancies and correcting underestimated gestational dates.

Anencephaly, spina bifida and encephalocele, collectively called neural tube defects, are important causes of fetal and infant death and usually result in a serious handicap to survivors. In Japan the incidence of this group of disorders in induced abortions was 5.6 per 1,000 or about five times the incidence at birth.[1] Creasy and Alberman[2] published very similar estimates (5.3 per 1,000) for London at eight weeks of gestation and concluded that about half would be aborted spontaneously by 28 weeks. Anencephaly is lethal; about 25 percent of anencephalic infants are born alive, and these die within hours or days of birth. About 85 percent of the spina bifida defects are "open" or lack a complete covering of skin or thick membrane[3]; of the infants with this defect, 8 percent are stillborn or die within one day of birth, and at least 80 percent of those who survive to 5 years of age are severely handicapped.[4] Encephalocele, the least common of the neural tube defects, carries a high risk for serious neurologic deficit and mental retardation.

There is a well-recognized geographic variation in the prevalence of neural tube defects. Using a dual ascertainment system, Sever and co-workers[5] reported the prevalence of neural tube defects in Los Angeles County during the period 1966 through 1972 as 1.1 per 1,000 births, comprising 0.50, 0.51 and 0.08 cases of anencephaly, spina bifida and encephalocele, respectively. The present birth rate in California is about 400,000 live births a year, which would result in about 440 new cases of neural tube defects each year in the state.

α-Fetoprotein is produced in the fetal liver, passes into the blood and is excreted via fetal urine into amniotic fluid. It reaches a maximum level of 3 mg per ml in fetal serum from 11 to 13 weeks of gestation. The fall after that time is probably a result of dilution, for the total amount continues to increase until about 30 weeks, levels off and then falls rapidly after 36 weeks gestation. α-Fetoprotein probably reaches maternal serum via the placenta and—at least when the level is elevated in amniotic fluid—across the fetal membranes.

Refer to: Crandall BF, Robertson RD, Lebherz TB, et al: Maternal serum α-fetoprotein screening for the detection of neural tube defects—Report of a pilot program. West J Med 1983 Apr; 138:524-530.

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An integumental defect of a fetus may promote the loss of serum proteins, including α-fetoprotein, into the amniotic fluid. Amniotic fluid α-fetoprotein levels decrease slowly by about 10 percent a week from 14 through 20 weeks gestation. Maternal serum α-fetoprotein levels increase by about 15 percent a week until 30 weeks, plateau for about four weeks and then fall steeply. Both amniotic fluid and maternal serum α-fetoprotein levels are gestational age dependent and abnormal levels may indicate fetal complications and other abnormalities in addition to neural tube defects.

Reports of several maternal serum screening programs have already been published. The first and largest report of 18,000 pregnancies screened in the United Kingdom identified about 80 percent of the cases of open spina bifida and 90 percent of the occurrences of anencephaly.[3] In the United States the largest study was from New York in which more than 17,000 pregnancies were screened. The incidence of open neural tube defects was 1.2 per 1,000, and 91 percent were identified by maternal serum screening.[6]

We report our experience with a voluntary maternal serum screening pilot program in California that was started in April 1978 and completed in December 1980. Our aim was to screen at least 10,000 unselected pregnancies during the second-trimester and examine the potential of maternal serum α-fetoprotein screening as a routine pregnancy test.

Methods

Laboratory Studies

α-Fetoprotein levels in both maternal serum and amniotic fluid were determined by radioimmunoassay using a double-antibody technique. We first established the normal range in each by measuring α-fetoprotein in at least 100 specimens per week of gestation from known, normal singleton pregnancies between 14 and 24 weeks. Dates were calculated by counting gestational weeks from the last menstrual period. Serum specimens collected, for example, 16 weeks plus four days were counted as 17 weeks' gestation. For maternal serum the median and 95th percentile (equivalent to about twice the median) were determined and for amniotic fluid the mean and standard deviations above and below this. In the second half of the study, acetylcholinesterase gel electrophoresis was done on all amniotic fluid specimens derived from women with elevated serum α-fetoprotein levels. We followed the recommendations of the National Committee for Clinical Laboratory Standards for monitoring our laboratory.[7] Intraassay variation did not exceed 5 percent and interassay variation 10 percent.

Office/Clinic Screening

Enrollment in the program was entirely voluntary. After an explanation concerning the purpose, method and limitations of maternal serum screening, women wanting the test were asked to complete a brief intake form, giving their name, height, weight, age, pregnancy and reproductive and family history. They were asked to read and sign an informed consent form (approved by the UCLA Human Subjects Protection Committee). The intake and consent forms were printed in both English and Spanish.

Specimen tubes were supplied to clinics and offices, and information requested on the label included the patient's name and identification of the physician or clinic, the last menstrual period or gestational date and the date the blood specimen was taken. Styrofoam mailers were supplied and these were returned with fresh supplies every one to two weeks. We requested that 6 to 8 ml of venous blood be obtained between 16 and 20 weeks of gestation and transferred to our laboratory within a week. Usually one office collected specimens with a single workweek and mailed them all to us at once. These were stored at 5°C until transfer and sent via US mail at ambient temperature. Serum α-fetoprotein levels were determined within one to three days of arrival in the laboratory.

Our results were returned to offices and clinics on a special form that shows our normal range on a graph. An abnormal result (a serum α-fetoprotein level $\geq$95th percentile) was telephoned to the office and, in addition, we sent a mailgram, retaining a copy of this. A second blood specimen was requested and a second telephone call was made if this was not received within a week. Sonography was recommended if maternal serum α-fetoprotein levels remained at or above the 95th percentile and in most instances this was done at UCLA. If an elevated level was satisfactorily explained by incorrect dates, the presence of twins or fetal death, no further action was taken. In some instances, a neural tube defect was detected but in these cases, as well as in those without an explanation, an amniocentesis was recommended for amniotic fluid α-fetoprotein measurement and, during the second half of the project, acetylcholinesterase gel electrophoresis. This was repeated unless a neural tube defect was unequivocally identified on the sonogram.

Patient Population

Initially we elected to test both clinic and private obstetrical patients. The former included women attending two US Navy hospitals and was therefore not a true clinic population. The majority (about 75 percent) of our population were women attending private obstetricians' offices. This was mainly because lack of personnel at the UCLA and other clinics limited counseling of pregnant women before obtaining an informed consent or because the first clinic appointment occurred after 20 weeks of gestation.

One of us (B.F.C.) was available to counsel any potential patient before the first blood test and to discuss with physicians and patients the reasons for elevated maternal serum α-fetoprotein levels, as well as to give recommendations for the future. Additional counseling was always provided when these women came in for a sonogram and amniocentesis. The proto-

col for our maternal serum screening project is shown in Figure 1.

The outcomes of pregnancies were obtained from medical charts and delivery records. These were coded and all information stored in a computer. Abnormal outcomes identified stillbirth, spontaneous abortion, birth weight and the presence of neural tube defects, hydrocephalus, other central nervous system abnormality, omphalocele, renal abnormality, gastrointestinal atresia and neonatal hepatitis. Additional abnormalities were recorded as "Other."

Results

In all, 10,715 pregnancies in the second trimester were screened for maternal serum α-fetoprotein levels and the completed pregnancy outcome, including the newborn examination, is known in 8,787. Of the 1,928 pregnancies whose outcome is unknown, 95 (4.9 percent) had one elevated maternal serum α-fetoprotein level. The number of women reaching each level of the protocol is shown in Table 1.

There were 14 cases of neural tube defect, of which 12 were open and 2 closed. In one of the latter there was a small lipoma over a 0.5 cm parietal bone defect with no subsequent neurologic deficit; in the other, an occipital encephalocele was covered by a full thickness of scalp. Of the 12 cases of open neural tube defects, six were anencephalic and six were spina bifida. The incidence of neural tube defects was 14 per 10,715 (about 1.3 per 1,000) or 1.1 per 1,000 for open neural tube defects (Table 2). One case of open spina bifida had a first maternal serum α-fetoprotein level at 16 weeks that was greatly elevated, but the second serum level at 19 weeks was well within the normal range and no sonography was done. A second case of open spina bifida occurred to a woman with an elevated maternal serum α-fetoprotein level whose second serum specimen was not submitted until after 24 weeks gestation and no further action was taken. One clinic elected to proceed directly to sonography instead of sending a second serum specimen as requested after a very high first maternal serum α-fetoprotein value. The sonogram was interpreted as normal, no further action was taken and an anencephalic infant was delivered at term. These problems are reviewed in the discussion.

The risk of a neural tube defect occurring at each step of the protocol is shown in Table 3. In no case of simple hydrocephalus was there an elevated maternal serum α-fetoprotein value. Pregnancies resulting in spontaneous abortions, stillbirth, neonatal deaths and birth weights of less than 2.5 kg are shown in Table 4. The incidence of spontaneous abortion or perinatal death was 4.8 times higher in women with one elevated serum α-fetoprotein level than in those with a normal level. Low serum levels were useful in identifying six

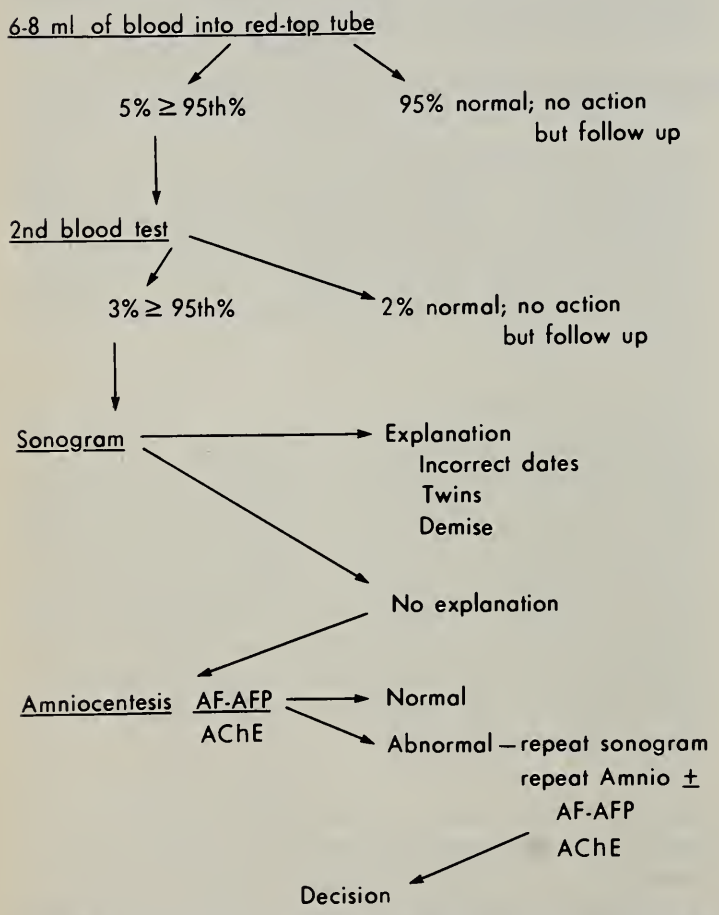

Figure 1.—Protocol for maternal serum screening. AF-AFP = amniotic fluid α-fetoprotein assay, AChE = acetylcholinesterase.

TABLE 1.—*Results of Maternal Serum α-Fetoprotein (MS-AFP) Screening in 10,715 Women*

Studies	*Number*	*Percent*
Normal first MS-AFP value	10,149	94.72
First MS-AFP ≥ 95th percentile	566	5.28
Second maternal serum taken	548*	5.1
Second MS-AFP ≥ 95th percentile and sonography done	353	3.3
Elevated MS-AFP level explained	187	1.7
Wrong gestational dates	140	...
Twins	42	...
Fetal death	5	...
Elevated MS-AFP level not explained	166	1.5
Amniocentesis done	151†	1.4

*Refused, 6; elected to have sonography, 4; too late for second MS-AFP, 8.

†Refused, 9; too late for amniocentesis, 5; anencephaly interpreted as normal sonogram, 1.

TABLE 2.—*Fetal Abnormalities Identified by Maternal Serum α-Fetoprotein (MS-AFP) Level**

Type of Abnormality	*No. of Cases With MS-AFP <95th Percentile*	*No. of Cases With MS-AFP ≥95th Percentile*
Anencephaly	0	6
Spina bifida (open)	0	6
Encephalocele	2	0
Hydrocephalus	4	0
Omphalocele	1	2
Gastrointestinal atresia	2	0
Renal abnormality	0	1
TOTAL	9	15

*Abnormalities listed as "Other" in our study included hypospadias, polydactyly, hip dislocation, cleft lip and palate, congenital heart defect and talipes but are not included here.

missed abortions as well as early gestational dates. Excluding twins, the risk of an infant weighing less than 2.5 kg was about three times higher in women who had an elevated maternal serum α-fetoprotein level than in women who had normal levels. Medical records frequently failed to distinguish prematurity from infants small for gestational age; these are reported together under low birth weight. There were no spontaneous abortions in the 151 women undergoing amniocentesis in this study. Women who had one elevated serum α-fetoprotein level had about an 80 percent chance of a normal pregnancy outcome and a 20 percent chance of an abnormal outcome. This compares with 95 percent and 5 percent, respectively, in those who had a normal maternal serum α-fetoprotein level (Table 4).

Discussion

The incidence of open neural tube defects in a population consisting mainly of private obstetrical patients in Southern California was 1.1 per 1,000. There were no true false-positives, defined as the termination of the pregnancy of a normal fetus. There were three known false-negatives, though all were identified by elevated first maternal serum α-fetoprotein levels. It is possible, though unlikely, that there were additional false-negatives in 1,928 pregnancies with unknown outcome. Two of three cases of omphalocele were also identified by maternal serum screening. None of the four cases of simple hydrocephalus resulted in elevated serum α-fetoprotein levels. One triplet pregnancy and 50 percent of twin pregnancies were identified by elevated maternal serum α-fetoprotein values. Of women with one elevated serum α-fetoprotein level, 4 percent experienced a spontaneous abortion or perinatal death occurred, and 12 percent were delivered of a baby weighing less than 2,500 grams, compared with 0.8 percent and 4 percent, respectively, in those with normal serum α-fetoprotein levels.

Positive and Negative Aspects of Maternal Serum Screening

The positive and negative aspects of maternal serum screening are listed in Table 5. In general, positive aspects were enough to convince many obstetricians to continue to offer maternal serum screening after this pilot project was completed. Although anencephaly is not compatible with survival after birth, most obstetricians and patients felt it was advantageous to identify these cases in the second trimester. Six women were diagnosed as having missed abortions because serum α-fetoprotein levels were in the normal adult range (<20 ng per ml). About 50 percent of twins were first identified by an elevated serum α-fetoprotein level, and the pregnancy management was consequently changed. In addition, the higher risk of a poor pregnancy outcome in women with one elevated serum α-fetoprotein level suggests the need for close supervision of these pregnancies.

The recommended time for the first maternal serum α-fetoprotein measurement is 16 to 20 weeks and this initially presented a problem. Private patients generally commence their obstetrical care early and most of the routine blood work is completed in the first trimester. Clinic patients, however, were frequently given their first appointment after 20 weeks. Personnel time necessary to discuss neural tube defects and maternal serum screening was a particular problem for clinics. Maternal anxiety resulting from one elevated serum α-fetoprotein level has been cited many times as a deterrent to widespread adoption of maternal serum screening. In this study it was particularly evident in the first year and required considerable counseling time. There was a noticeable decline in the second year, however, and this seemed to result from better preparation of women, before the first blood test, for possible outcomes and the decisions required. Many obstetricians

TABLE 3.—*Observed Risk of Open Neural Tube Defect Occurring at Each Step of Maternal Serum Screening*

Level in Protocol	*Observed*	*Risk*
Risk in general population	1.1/1,000	1.1/1,000
Risk after 1st ↑ MS-AFP level	12/566	1/47
Risk after 2nd ↑ MS-AFP level	9/353	1/39*
Risk at amniocentesis	9/151	1/17

MS-AFP = maternal serum α-fetoprotein; ↑ = elevated.

*The second MS-AFP level was normal in one case of open spina bifida, too late in a second case of open spina bifida and omitted in one case of anencephaly.

TABLE 4.—*Spontaneous Abortions, Perinatal Deaths and Low Birth Weight in 8,787 Pregnancies Screened by Maternal Serum α-Fetoprotein Assay (MS-AFP) With Known Outcomes*

	No. of Cases With MS-AFP <95th Percentile		*No. of Cases With MS-AFP ≥95th Percentile*	
Condition	*Number*	*Percent*	*Number*	*Percent*
Outcome known	8,316		471	
Normal	7,931	95.4	382	81.1
Abnormality	9	0.0	15	3.2
Spontaneous abortion*	18		4‡	
Stillbirth	28	0.9	7§	4.0
Neonatal death	25		8§	
Birth weight <2,500 grams†	305	3.7	55§	11.7

*Occurring by 20 weeks gestation or if fetus weighs <500 grams.
†Does not include those listed as spontaneous abortion, stillbirth or neonatal death.
‡$P = <.01$.
§$P = <.001$.

TABLE 5.—*Positive and Negative Aspects of Maternal Serum Screening*

Positive	*Negative*
Detection of neural tube defect	Time of blood test (at 16 to 20 weeks)
Detection of other abnormalities	Clinic/physician time
Detection of missed abortions	Maternal anxiety
Early identification of twins	Increased sonography
Correction of gestational dates	Increased amniocentesis
Improved pregnancy management	False-positives
	False-negatives
	Spontaneous abortion after amniocentesis

preferred to include this with a discussion of the general pregnancy management during the initial appointment.

In 3.3 percent of women in this study a sonogram was needed, and it should be stressed that first-level sonography (defined as the level available in the average obstetrician's office or community hospital) should only be used to determine gestational age, identify the presence of a multiple pregnancy or the absence of a fetal heartbeat. If none of these three reasons for an elevated serum α-fetoprotein level are found, amniocentesis should be recommended. Application of this rule would have avoided the term delivery of an anencephalic infant to a woman whose sonogram was interpreted as normal after the first serum α-fetoprotein value was elevated. All amniotic fluid specimens should be tested by α-fetoprotein assay and acetylcholinesterase gel electrophoresis. We have had no false-negatives using this combination.[8] Although we included chromosome studies on all amniotic fluid specimens, this is probably unnecessary unless there are additional indications such as maternal age. No chromosome abnormalities were detected in 151 amniotic fluid specimens. We believe, however, that this option should be available to those wanting it.

One major criticism of maternal serum screening is its nonspecificity, so that a large number of false-positives occur at the first blood test (98 percent). This figure can be diminished by adopting a higher cutoff level, but this decreases the sensitivity, particularly for open spina bifida. True false-positives are very unlikely, and none occurred in this program. In our experience with 13,000 amniotic fluid specimens, equivalent to about 800,000 women undergoing maternal serum screening, the addition of acetylcholinesterase gel electrophoresis in which amniotic fluid α-fetoprotein levels measured $\geq +2$ SD above the mean would have prevented two true false-positives. Patient anxiety leading to the premature termination of a normal pregnancy after one elevated maternal serum α-fetoprotein level did not occur in this series. False-negatives are a far greater concern and can be expected in about 20 percent of cases of open spina bifida.[3] Our experience of one case of open spina bifida with an elevated first maternal serum α-fetoprotein level, followed by a normal second serum α-fetoprotein level, was particularly distressing and raises the question of why a second normal laboratory result should be accepted instead of the first one, which is abnormal. This has been addressed in a recent publication,[9] with the conclusion made that there was little value in testing a second maternal serum specimen if the first showed a high or borderline value. If all women are referred for sonography after one elevated serum α-fetoprotein level, however, a great increase in the number of these studies done can be anticipated. We have tended to compromise by offering sonography when the first serum α-fetoprotein level was at or above the 97th percentile. Lastly, the risk of pregnancy loss after amniocentesis is mentioned frequently as a deterrent to widespread maternal serum screening; in our hands, this has been less than 0.5 percent and probably about 0.3 percent. No case occurred in this study.

Follow-up of Surviving Infants Who Have Spina Bifida

Althouse and Wald[4] reported the follow-up of 213 cases of spina bifida cystica, of which 102 had open and 32 closed defects of the spine only. The remaining 79 cases affected the head or were unclassified. Of the infants with open spina bifida, 36 percent survived to 5 years of age, 59 percent had normal intelligence and only 8 percent had no handicap. Of the cases of closed spina bifida 60 percent survived to 5 years and about a third had no handicap, a third were moderately and a third severely handicapped. Nonselective surgical treatment was used in the first two years and selective surgical treatment in the last five years of their study. These findings tend to substantiate those of Laurence[10] and show that nonselective surgical care resulted in more five-year survivals but a larger proportion with serious handicaps. Sadovnick and Baird[11] reported that 40 percent of infants who had spina bifida survived beyond age 7 years in British Columbia with nonselective surgical care, a figure close to the five-year survival in Oxford. The survival curve reached a plateau between 7 and 30 years, after which morbidity and mortality increased because of renal failure.

Recommendations for Maternal Serum Screening in California

Low-Risk Population

Office or Clinic. Of infants who have neural tube defects, 95 percent are born to couples with no prior history of these defects either in themselves or their children. We believe the advantages of screening outweigh the disadvantages in this population, and maternal serum screening should be offered on a voluntary basis to all pregnant women.

Literature concerning the test and the frequency and seriousness of cases of neural tube defect should be available in English and Spanish (and other languages where indicated) in clinics and offices. Additional information may be given individually or in groups to private and clinic patients. Although it is not necessary for women to read and sign a consent form, all patient records should indicate that a woman was offered maternal serum screening and requested or declined it.

Ideally, one person in an office or clinic should be responsible for obtaining blood specimens during the 16 to 20 weeks of gestation and supervising their transfer to the appropriate laboratory.

Laboratory. α-Fetoprotein laboratories should have experience with α-fetoprotein radioimmunoassays. They should have established their own normal maternal serum and amniotic fluid α-fetoprotein ranges between 15 and 22 weeks gestation. It is not sufficient to adopt the normal range of another laboratory as these vary widely. Assays should be done within two to three days of receipt of the specimen. A second blood specimen should be requested if the maternal serum α-fetoprotein

TABLE 6.—*Risk of Neural Tube Defects Occurring in Relatives per 1,000*

Source	Incidence in General Population per 1,000	Children of				2nd Degree Relatives†
		Mother's Sisters	Mother's Brothers	Father's Sisters	Father's Brothers	
Lippman-Hand et al[12]	3.31	13.2(4.0)*	2.6(0.8)*	6.0(1.8)*	4.0(1.2)*	4.1(1.2)*
Zackai et al[13]	1.70	9.9(5.8)	2.2(1.3)	3.2(1.9)	1.8(1.0)	...

*Multiples of general population risk.
†Includes half sibs of proband and mother's and father's siblings.

level is at or above an agreed cutoff level and a reminder should follow if this is not received within seven to ten days.

First-level sonography is recommended if the second serum α-fetoprotein level remains elevated and this should determine the gestation date and identify a twin pregnancy and a live fetus only. If neither is identified, referral should be made in the usual way for counseling and amniocentesis. All amniotic fluid specimens should be tested by α-fetoprotein assay and acetylcholinesterase gel electrophoresis and this should be repeated if abnormal before a decision is made concerning termination of the pregnancy.

The timing and complexity of interpretation distinguish maternal serum screening from other laboratory tests. A trained coordinator to interpret results and convey recommendations to offices, clinics and patients is essential and this person can be shared among several maternal serum screening laboratories.

High-Risk Population

This group includes persons who have open spina bifida or spina bifida occulta and vertebral abnormalities affecting more than one vertebra, couples who have had a previous child with such defects or where the mother's sister's child is similarly affected. The risk is 3 percent for the occurrence of a neural tube defect in the former and four and six times the general population risk in the latter (Table 6). Amniocentesis for amniotic fluid α-fetoprotein assay and acetylcholinesterase gel electrophoresis is recommended for this high-risk population.[8]

Expected Result of Maternal Serum Screening in California

Cases of Neural Tube Defect Identified

Sever and associates[5] found the prevalence of neural tube defects in Los Angeles County was 1.1 per 1,000 total births, of which 0.51 per 1,000 had spina bifida. If the same prevalence pertains throughout the state of California where the birth rate was about 400,000 live births in 1981,[13] 204 infants with spina bifida, of which about 173 will be open, will be born in one year. The British collaborative study reported that about 80 percent of the cases of neural tube defect were identified. Therefore maternal serum screening should identify about 138 cases of neural tube defects per year in California. The expected outcome of such a maternal serum screening program is shown in Table 7.

TABLE 7.—*Expected Results of a Statewide California Program**

Time	Cases of Neural Tube Defect	
	Number	Percent
Expected at delivery	436	100
Anencephaly	200	
Spina bifida	204	
Closed	31	
Open	173	
Encephalocele	32	
Identified at maternal serum screening†	318	73
Anencephaly	180	90
Open spina bifida	138	80

From National Center for Health Statistics, 1982.[14]

*100 percent compliance based on 400,000 live births per year.
†Number of cases of encephalocele not known.

TABLE 8.—*Results of Maternal Serum Screening in California**

Maternal Serum α-Fetoprotein (MS-AFP)	Number of Pregnancies	Percent
1st blood test	400,000	100
Elevated 1st MS-AFP level	20,000	5
Elevated 2nd MS-AFP level, requires 1st-level sonogram	12,000	3
Elevated 2nd MS-AFP level explained†	6,000	1.5
Elevated 2nd MS-AFP level not explained, referred for 2nd-level sonogram and amniocentesis	6,000	1.5

From National Center for Health Statistics, 1982.[14]

*Based on 100 percent compliance and 400,000 live births per year.
†For example, incorrect gestational dates, twins and fetal death.

Availability of Resources

Laboratory. We have estimated that a laboratory doing maternal serum α-fetoprotein assays and using one technician can do about 400 assays a week. With total patient compliance, 400,000 first serum and 20,000 (5 percent) second serum specimens can be anticipated and would require the services of about 20 laboratories so equipped.

Sonography and Amniocentesis. Of the total maternal serum α-fetoprotein assays done, 3 percent, or 12,000 patients, will require further study. It is not anticipated that these 12,000 first-level sonographies will create a stress on existing resources because many women now have at least one sonogram done sometime during their pregnancy. Second-level fetal sonography refers to the level of expertise expected in tertiary care hospitals or amniocentesis centers classified as class A by the California State Department of Health Services, Genetic

Disease Branch. About 50 percent, or 6,000 patients, having first-level sonography will require referral to these centers (Table 8). This translates into a 40 percent increase in patient load for amniocentesis centers and amounts to about 300 additional patients per center per year or six a week. This increase could be a problem for some, if not all, centers. However, these calculations are based on 100 percent use of maternal serum screening, a most unlikely event.

Because women referred for amniotic fluid α-fetoprotein assay require counseling and because the diagnosis of a neural tube defect usually depends on sonographic interpretation as well as the results of α-fetoprotein and acetylcholinesterase studies, these tests are probably best done in amniocentesis centers. We have already indicated that chromosome studies are an optional additional test.

Cost-Benefit Estimate. We have not attempted to include an estimate of cost and benefit in this report. Layde and colleagues published an analysis for the Atlanta area wherein the incidence of neural tube defects (anencephaly and spina bifida) was 1.73 per 1,000 births.[15] A theoretic cohort of 100,000 pregnant women was examined and a cutoff of 2.5 times the median (between the 96th and 97th percentile) selected. A second serum specimen was required in 3.7 percent of cases, sonograms in 2.6 percent and amniocentesis in 1.9 percent. Chromosome analysis of amniotic fluid cells was omitted. The calculated cost was about $2 million, or slightly over $20 per woman screened. The total economic benefits exceeded $4 million, or about $82,000 per case of spina bifida prevented.

Sadovnick and Baird estimated lifetime care in a case of spina bifida averaged about $84,000 in 1980 dollars.[11] They concluded that a maternal serum screening program would be cost-effective in British Columbia, where the prevalence of neural tube defects is 1.55 per 1,000 live births.

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Results of Neurosurgical Microvascular Extracranial-Intracranial Bypass for Stroke: A Decade of Experience

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In 400 patients who have had neurosurgical microvascular bypass operations by one surgeon for problems of cerebrovascular occlusion disease, the results are encouraging, particularly in those who had transient ischemic attacks with hemodynamic lesions previously considered inoperable or inaccessible. The permanent neurologic morbidity rate is 2 percent and the present operative mortality is 2.5 percent. The incidence of stroke to date on the side of a functioning bypass is 0.9 percent per year. Average duration of follow-up is 43 months.

Postoperative angiograms show that a bypass operation designed to prevent strokes by bypassing thrombi in the internal carotid artery "is a surgical success," says Dr Henry Barnett, Chairman of Neurological Sciences at the University of Western Ontario [Faculty of Medicine, London, Ontario].

Medical Tribune, May 1982

In the past decade a number of papers have described the preliminary indications and early results of a neurosurgical microvascular bypass operation designed to increase the collateral blood supply in problems of occlusive cerebrovascular disease.[1-7] This surgical approach was originally developed by Yasargil and Donaghy in 1967.[8,9] The symptoms in patients who met the criteria for the surgical procedure were felt to be due to hemodynamic insufficiency rather than embolic episodes. The surgical technique was described and, though the initial results were promising, a longer follow-up time was required to observe the effect of microvascular bypass operations on the future clinical course of these patients. It also was felt necessary to evaluate the patency rates of the surgical bypass postoperatively in a larger series of patients than those previously presented.[10]

This paper describes the results in 400 patients who have undergone this microvascular bypass procedure and whose cases have been followed for six months to ten years postoperatively (see Table 1). Most patients in the group reported here were suffering from transient ischemic attack or had suffered a "completed stroke" with pronounced recovery and a subsequent mild residual neurologic deficit (Table 2). Arteriographic findings are shown in Table 3.

Cerebrovascular Occlusive Disease and Arteriographic Findings

In patients in whom transient ischemic attacks have developed, there is a 6 percent to 12 percent chance per year of a completed stroke occurring.[11-14] The primary aim of stroke therapy, therefore, is to prevent such a disaster and, if possible, to improve the quality of life.

An analysis of 123 consecutive patients presenting with transient ischemic symptoms at a university vascular clinic showed that 19 percent (N=23) had a completely occluded internal carotid artery as the cause of the hemodynamic cerebrovascular insufficiency. In a short follow-up period 3 of the 23 patients suffered a completed stroke.[15]

In a national cooperative study, arteriographic investigation showed that 6 percent of the patients studied had completely inaccessible lesions in the cerebral vasculature.[16] An additional 16 percent of patients studied for cerebrovascular symptoms were shown to have old, complete, internal carotid artery occlusions, which at present are considered inoperable because of the low success rate of reopening the vessel.[17,18] Therefore, in 22 percent of patients studied by arteriography, lesions inoperable or inaccessible with present conventional surgical techniques may be present. This amounts to potentially several thousand persons per year present-

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ing with transient ischemic attacks who do not have a permanent neurologic deficit.

Current Indications for Surgical Operation

Indications for the microvascular bypass procedure fall into two categories: lateralized low-perfusion syndromes and generalized low-perfusion syndromes.

Lateralized Low-Perfusion Syndromes

The symptoms in this category depend on the vessel involved (usually the middle cerebral artery) and the functional collateral supply available. The symptoms may be transient, progressive or fluctuating.

There are several types of causes, including the following:

- Old internal carotid artery occlusions with poor collateral blood supply.
- Carotid artery stenosis with poor collateral blood supply due to atherosclerosis or vasculitis.
- Middle cerebral artery occlusions with mild or moderate deficit and absent recanalization, plus poor collateral blood supply.

TABLE 1.—*Summary of Patient Characteristics for Those Who Had Bypass Procedures, 1971 Through 1981*

Number of cases	400
Men	75%
Women	25%
Age 65 years or more, retirement years	33%
Age 65 years or less, working years	66%
Average age preretirement, most patients in late 50s	57
Minimum duration of follow-up	6 mos
Average duration of follow-up	43 mos

TABLE 2.—*Types of Clinical Presentation of Patients Who Require Bypass Procedure*

Neurologic Deficits	*Patients (N=400)* Number	(Percent)
TIA* or RIND†	240	(60)
"Completed stroke," mild,‡ plus TIA	81	(20)
Progressive stroke§	26	(7)
Other	53	(13)

*TIA=transient ischemic attack: neurologic dysfunction for less than 24 hours with complete recovery.
†RIND=reversible ischemic neurologic deficit: neurologic dysfunction for more than 24 hours with complete recovery.
‡Clumsiness of hand or leg fluctuating at times, with fluctuating dysphasia.
§Progressive loss of neurologic function.

TABLE 3.—*Summary of Arteriographic Findings*

Arterial Lesions	*Patients* Number N=400	(Percent)
Bilateral internal carotid artery occlusion	36	(9)
Internal carotid artery occlusion	128	(32)
"Siphon" stenosis, cavernous portion of carotid artery	85	(21)
Multiple vessel occlusions and stenoses (intracranial or extracranial)	44	(11)
Middle cerebral artery stenosis	38	(10)
Middle cerebral artery occlusion	12	(3)
Other (aneurysm, vertebrobasilar lesion, tandem lesions)	57	(14)

- Vertebral and basilar artery stenotic lesions with poor collateral blood supply.[19]
- "Inoperable" giant intracranial aneurysms due to inadequate supply of collateral vessels.[20]

Generalized Low-Perfusion Syndromes

There is a smaller group of patients who suffer from a generalized ischemic cerebrovascular syndrome due to occlusive disease of multiple large vessels. In these persons symptoms such as dizziness, incoordination, blurred vision, syncopy, dementia and transient motor, speech or sensory deficits may be noted.

Two causes may be given in this category, as follows: multiple vessel occlusions and multiple-vessel inaccessible stenoses.

Analysis of Results

Transient Ischemic Attacks

A significant percentage (86 percent) of patients suffering from transient ischemic attacks had symptomatic relief following the surgical bypass operation (Table 4). Therefore, the quality of their lives is improved.

Late Stroke Incidence

At the Mayo Clinic investigators have extensively followed a series of 200 patients suffering from clinically definite transient ischemic attacks. In the Mayo Clinic group the stroke occurrence rate after 16 months was 22 percent.[13] In our series to date (average duration of follow-up, 43 months) the incidence of stroke occurring is 0.9 percent per year on the side of a patent bypass

TABLE 4.—*Results of Clinical Therapy to Date (Average Duration of Follow-up, 43 Months)*

Neurologic Deficits	*Number of Patients N=347**	*Asymptomatic or Improved Number (Percent)*
Transient ischemic attack or reversible ischemic neurologic deficit†	240	206 (86)
Progressive loss of neurologic function	26	16 (60)
"Completed stroke," mild‡	81	41 (51)

*The 53 patients who had deficits that fell into a miscellaneous category were not included in this table.
†One or no transient ischemic attack postoperatively (see Table 2 for further definition of terms).
‡Patients had objective evidence of postoperative improvement in speech, writing and daily tasks (see Table 2 for further definition of terms).

TABLE 5.—*Summary of Complications of Bypass Procedure*

Complications	*Patients* Number N=400	(Percent)
Morbidity (permanent)		
Permanent increase in deficit, moderate parietal lobe dysfunction	9	(2.2)
Wound infection, surgical repair required	1	(0.2)
Marginal scalp ischemia, no surgical procedure required	5	(1.2)
Subdural hygroma and hematomas, all evacuated uneventfully	7	(1.8)
Mortality		
Operative (death within 30 days)	10	(2.5)

TABLE 6.—*Postoperative Patency Rates of Bypass Procedure*

	Percentage of Patients N = 400
Doppler ultrasound auscultation over bypass	100
Apparently open	96

TABLE 7.—*Cause of Late Deaths (93 of 400)*

Cause of Death	*Number N = 93*	*Percent*
Heart attack	47	51
Stroke	23	25
Other	18	19
Unknown	5	5

(nine strokes per 300 survivors per 3.5-year follow-up). The incidence of all types of strokes (operative, late hypertensive hemorrhagic, contralateral or basilar) is 2 percent per year (32/400). It may be that in the future bilateral surgical arterial bypass procedures should be pursued more aggressively in patients with disease of multiple vessels. The improvement rate in cases of progressive and mild completed stroke appears to be significant (see Table 4). In this group these statistics, of course, must be viewed cautiously, as the natural history of spontaneous improvement in completed strokes is quite variable (Tables 5 and 6).

Discussion

Ten deaths occurred within the 30 days after the surgical operation. The mortality of the procedure was therefore 2.5 percent. Patency rates of the bypass postoperatively were 96 percent (Table 6). In this series of 400 patients the primary cause of *late* death was cardiac (Table 7).

Many investigators have reported that substantial improvement in regional cerebral blood flow followed such a bypass procedure (allowing for the intrinsic errors implicit in the methods used).[6,21,22] Other workers have reported a significant increase in retinal artery perfusion pressures following bypass operation for symptomatic internal carotid artery occlusions.[23]

Objective evaluation of the effects of any relatively new operation is difficult to obtain. The ultimate test of whether this particular operative approach is useful clinically will be a comparison between similar groups of patients (those operated on versus those not operated on) suffering from angiographically shown inaccessible or inoperable cerebrovascular stenotic or occlusive lesions. Such a study is now in progress. A report of the outcome will be available in about two years.

These results—though obviously not a randomized study—suggest that this operation may find a permanent place in the neurosurgical armamentarium of the future. In comparison with the available statistics on the natural history of cerebrovascular occlusive disease, the incidence of late stroke appears to have been significantly lowered.

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Medical Progress

The Toxicology of PCB's—An Overview for Clinicians

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Polychlorinated biphenyls (PCB's) have low acute toxicity but are of public health concern because of their persistence in the environment, the bioaccumulation in human and animal tissues, and their potential for chronic or delayed toxicity.

Although many questions remain unanswered, it is clear that occupational exposure, at a minimum, can produce dermatologic effects and liver dysfunction. The long half-life of PCB's and their presence in various human tissues leaves open the possibility of substantial chronic and delayed effects analogous to those seen in animals. PCB's are potent inhibitors of reproductive function in both rodents and nonhuman primates and produce liver tumors in animal cancer bioassays. As potent inducers of hepatic enzyme systems, PCB's may have additional unpredictable long-term health effects.

These effects have only recently begun to be studied in a rigorous manner, and although the epidemiological evidence is neither complete nor entirely consistent, there can be no question of the necessity to keep human exposures to the lowest feasible levels.

The last decade has been noteworthy for an increased awareness and concern about the presence of toxic chemicals in the environment. Polychlorinated biphenyls (PCB's) have been particularly notorious in this regard. In fact, it was the discovery of major environmental contamination with PCB's that led to passage of the Toxic Substances Control Act in 1976. By 1977, the Environmental Protection Agency had developed elaborate regulations that banned the further manufacture of PCB's and PCB-containing equipment and strictly controlled the handling, storage and disposal of existing PCB's. As a result of increased public awareness and more extensive regulatory activity, primary care physicians and public health practitioners are regularly confronted with rather sophisticated questions regarding health risks associated with exposure to these chemicals.

This article was written to guide the practicing physician through the morass of literature currently available on the subject of PCB's, with the more specific aim of offering a rational approach to the evaluation and medical work-up of patients who present with a history of PCB exposure.

The Hazard Evaluation System and Information Service, in the California State Departments of Health Services/Industrial Relations, has recently published a review of PCB toxicology with emphasis on potential human health effects resulting from occupational exposures to PCB's.[1] This article will summarize that more lengthy document with an expanded section on the problems of biologic monitoring and medical surveillance. For a more detailed description of the various aspects of PCB toxicology, the reader is referred to a number of published reviews.[2-8]

Chemistry

It is important to any discussion of the toxicology of PCB's to appreciate some essential facts regarding their chemistry. PCB's belong to the class of halogenated aromatic hydrocarbons, all of which are foreign to biologic systems. (There are many confirmed or suspected carcinogens in this chemical class.) PCB's are actually a family of chemicals with varying numbers and positions of chlorine atoms attached to a biphenyl nucleus (see Figure 1). Commercial products are always mixtures of chlorinated biphenyls and are de-

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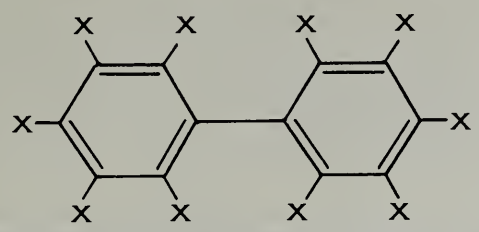
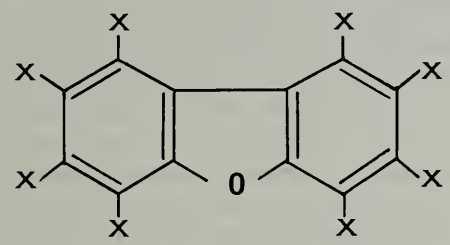
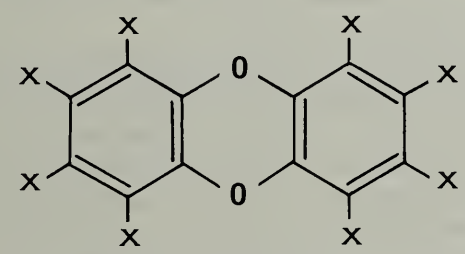


POLYCHLORINATED BIPHENYLS
(PCB's)



CHLORINATED DIBENZOFURANS
(PCDF's)



CHLORINATED DIBENZODIOXIN

Figure 1.—Polychlorinated biphenyls are a family of chemicals with varying numbers and positions of chlorine atoms attached to a biphenyl nucleus. They belong to a class of halogenated aromatic hydrocarbons, all of which are foreign to biologic systems.

scribed according to the percent of chlorine in the mixture. For example, Aroclor 1242 is the trade name for the Monsanto product with an average of 42 percent chlorine content. The degree of chlorination, and more particularly the isomeric structure, affects a number of biologic variables including rate of metabolism and excretion.

There is another important fact crucial to interpretation of toxicologic data on PCB's: all commercially produced PCB's are contaminated with the polychlorinated dibenzofurans (PCDF's) (see Figure 1). The degree of contamination varies somewhat with different commercial products, but is generally in the range of a few parts per million or less.

Contamination by polychlorinated dibenzofurans is of particular concern because their toxicity is much greater than that of PCB's in comparative animal studies, and because of the structural similarity of these compounds to the highly toxic dibenzodioxins (see Figure 1). The pattern of observed effects in animals exposed to polychlorinated dibenzofurans closely resembles that seen following exposure to 2,3,7,8-tetrachlorodibenzodioxin (TCDD).[9]

Uses

PCB's were introduced into industry in the early 1930s. They have been used in a variety of ways because of their remarkable properties, including chemical stability, low volatility, nonflammability and high dielectric constants. Major uses have included heat exchange and dielectric fluids in transformers and capacitors, hydraulic and lubricating fluids, diffusion pump oils, plasticizers for plastics and coatings, ingredients of caulking compounds, printing inks, paints, adhesives and carbonless paper, flame retardants and extenders for pesticides.

Environmental Contamination

PCB's are chemically inert, and at least the more highly chlorinated members are resistant to metabolic transformation. Consequently, they are "biomagnified" in food chains and have been found in tissues of fish, wildlife and humans. PCB's have been identified as ubiquitous contaminants of water, air, land and aquatic sediments, even occurring in remote arctic areas far from disposal sites.

Because of persistence in the environment and biomagnification in the food chain, trace amounts in human blood, fat and milk have been documented in more than 50 percent of people sampled in all geographic areas of the United States. The "background" levels in human serum are typically less than 20 parts per billion. Levels reported from adipose tissue are somewhat greater, in the range of 1 to 2 parts per million, and residues measured in human milk have ranged from 40 to 100 parts per billion in whole milk.[10]

Significantly higher levels have been documented in sports fishermen consuming fresh water fish from contaminated streams and lakes and in certain occupationally exposed workers.[4,10]

As a consequence of the 1977 Environmental Protection Agency's ban on further manufacturing of PCB's occupational exposures to and environmental contamination by these compounds have been drastically reduced. Since a significant number of large transformers and capacitors currently in use were manufactured before 1977, there remains, however, (and will remain for some time) a continued potential for exposure in particular occupational groups. Utility workers, for example, may experience sporadic but potentially heavy exposures when cleaning up spills or when servicing and dismantling transformers and capacitors that still contain PCB fluid. Electricians, appliance service workers and firefighters also may have continued occupational exposure. The National Institute for Occupational Safety and Health (NIOSH) estimates that 12,000 workers have potential exposure as a result of current uses of PCB's.[6]

Pharmacokinetics

There is a striking lack of pharmacokinetic data available on PCB's. However, certain generalizations can be made on the basis of available animal data:[9]

- Absorption occurs by all routes (skin, gastrointestinal, inhalation).
- Distribution is primarily into fat.
- The liver is the primary site of biotransformation which is via hydroxylation and conjugation with glucuronic acid.
- Metabolism and excretion are dependent on specific molecular structures. Two adjacent unsubstituted positions facilitate biotransformation and excretion so that rates vary inversely with percent chlorination.
- Excretion is, in general, quite slow so that bioaccumulation occurs even at low exposure levels.
- There are essentially no pharmacokinetic data in humans. It is not known, for example, if intermittent high doses are more or less hazardous than low level chronic exposures to the same total dose.

A few generalizations can be made based on epidemiologic studies reporting PCB blood levels: The higher the exposure levels, the higher blood concentration of PCB's; and the higher the environmental concentration or the longer the period of exposure (or both), the longer the blood levels of PCB's remain elevated.[11-15] PCB levels have also been correlated with race and geographic residence and with age and dietary intake of fish.[16]

Human Toxicology and Epidemiology

Few good epidemiologic studies of the health effects of PCB's are available. Most studies reported in the literature have been characterized by one or more of the following shortcomings: (1) small study populations, (2) lack of accurate exposure data, (3) simultaneous exposure of workers to other potentially harmful chemicals and (4) lack of control for confounding variables, such as alcohol consumption.

In spite of these problems, some health effects have been consistently reported in studies of workers occupationally exposed to PCB's. In addition, a large-scale poisoning which resulted from ingestion of PCB-contaminated rice oil has been well documented and resulted in multiple signs and symptoms attributed to PCB's (or contaminants such as polychlorinated dibenzofurans, or both) (see *"Yusho"* below).

The health effects identified in a review of the epidemiologic literature are summarized below.

Acute Toxicity

PCB's have very low potential for producing acute toxic effects. In rodents the acute oral LD_{50} ranges from 1 to 10 *grams* per kg of body weight. According to the American Industrial Hygiene Association classification for acute toxicity, PCB's are classified as "slightly toxic to practically nontoxic." The low order of acute toxicity in experimental animals is consistent with the lack of acute effects observed in workers exposed to PCB's. Reported symptoms after occupational exposures include mild irritation of the skin and eyes at air levels above 0.1 mg per cu meter with unbearable irritation occurring above 10 mg per cu meter.[17] Systemic symptoms of nausea and headache have been reported but may be caused by the solvents (such as trichlorobenzene) in the PCB mixtures.

Dermatologic Effects

Exposure to PCB's (as well as certain other halogenated cyclic compounds including dibenzofurans and dibenzodioxins) has been associated with a specific skin rash commonly referred to as *chloracne*. Although it may resemble typical adolescent acne, there are certain distinct features: The most distinctive lesion is cystic, skin colored and measures from 1 to 10 mm. The other prominent lesion is the comedo. The comedones and cysts can become inflamed and secondarily infected with large pustules. Unlike adolescent acne, chloracne may occur at any age and may involve trunk, arms and legs as well as face, neck and back. It can be very persistent and refractory to treatment (for review see Crow[18]). A skin lesion exactly like chloracne has been observed in a number of species of animals experimentally exposed to PCB's.[19]

For many years it was believed that chloracne was due to external contact rather than systemic absorption of acnegenic agents. However, ingestion of PCB's without skin contact has caused chloracne in episodes of human poisoning, as well as in experimental animal studies.[8(chap 9C)]

Liver Damage

Abnormal findings on liver function tests have been reported in a number of occupational studies, and clinical hepatitis was observed in the *Yusho* epidemic (see below). However, some of the earlier investigators reporting abnormal liver function did not control for exposure to additional chemicals, previous medical histories or drinking patterns. Some marginal differences observed could have been related to these confounding variables. In a recent cross-sectional survey, Fischbein and co-workers[20] found no significant differences in liver function test results between capacitor manufacturing workers with low-level chronic exposure and nonexposed controls. However, in another cross-sectional study abnormalities were shown on liver function tests and seemed to correlate with serum PCB levels. With the exception of a few cases of chloracne, these workers had no other symptoms, signs or laboratory abnormalities.[21]

Liver damage, documented histologically, is the most consistent finding among the many laboratory animal species tested. Effects of low-level chronic exposure do show appreciable variation among species, but liver damage has been observed in all species and is usually the most sensitive indicator of PCB exposure.[1] The fact that liver dysfunction has been inconsistently observed in humans may be an artifact of the relative insensitivity of the standard liver function tests—aspartate aminotransferase (formerly known as SGOT) and ala-

TABLE 1.—*Clinical Presentation of* Yusho

1. History of ingestion of *Kanemi* rice oil.
2. General symptoms (more than 25 percent of the patients)
   Fatigue, headaches, increased sweating (palms), itching, transient visual disturbances, numbness of the limbs, swelling and pain in the joints, coughing, intermittent abdominal pain, menstrual changes.
3. Signs
   Skin/mucous membrane: acneform eruptions, comedones, distinctive hair follicles, pigmentation (skin, conjunctiva, gingiva, nails).
   Ocular: swelling, hypersecretion of the Meibomian glands, palpebral edema, hyperemia of conjunctiva.
   Systemic: jaundice (approximately 10 percent of patients), sensory neuropathy, bronchitis-like signs, bursitis, growth retardation, abnormal teeth (children).
4. Laboratory
   Unusual patterns and concentrations of PCB's in blood, increase of neutral lipids, hypoalbuminemia, anemia, lymphocytosis, decreased sensory nerve conduction velocity, adrenocortical hypofunction.

*Adapted from Kuratsune M: Yusho, chap 9B1 *In* Kimbrough.[8]

nine aminotransferase (formerly SGPT) determinations —as compared with biopsy and histologic analysis.

Yusho

Yusho is a Japanese word that means "rice oil disease" and refers to a poisoning epidemic caused by ingestion of cooking oil contaminated with PCB's and polychlorinated dibenzofurans. The episode occurred in western Japan in 1968 and affected more than 1,600 people.

Epidemiologic surveys of affected persons identified a particular brand of rice oil produced in early February 1968 as the causative agent. Subsequent analysis of the rice oil confirmed that it was contaminated with a large amount of Kanechlor 400 (Japanese brand of PCB's with 48 percent chlorine content), and components of Kanechlor 400 were also found in various tissues of patients.[22] The clinical features of patients with *Yusho* are well summarized in the diagnostic criteria as presented in Table 1. Both dermal and systemic effects are well documented with multiorgan system involvement in most patients.[23]

It is not clear how much the effects observed in *Yusho* victims can be extrapolated to current occupational and environmental exposures for the following reasons:

- The average amount of PCB ingested was estimated to be 2 grams and the minimum 0.5 gram.[24] This is a higher dose than would be expected from most occupational exposures. In addition, the PCB's were ingested as opposed to inhaled or skin-absorbed as is the case with occupational and environmental exposures.
- Frying of foods with the rice oil could have produced new compounds which may have altered the toxicity of the PCB's or the toxicity of possible contaminants.
- *Yusho* oil was shown to contain relatively high concentrations of dibenzofurans and quarterphenyls.[22]

Reproductive Effects

The *Yusho* incident is also important because it clearly documents the potential for reproductive and fetotoxic effects in humans. Two of the *Yusho* mothers had stillbirths; 10 of 13 babies had abnormal skin pigmentation, 9 of 13 had ocular discharge and 12 of 13 were small when compared with the national average. Although a variety of other effects were observed in these infants, follow-up of these children has shown no persistent morphologic or behavioral abnormalities.[22,23]

Adverse reproductive effects of PCB's have also been found in many mammalian and avian species.[25-31] The pattern of reproductive effects includes alterations in estrus cycles, failure of implantation, increased frequency of spontaneous abortions, low birth weight offspring and decreased postnatal survival. No specific teratogenic effects of PCB's have been observed in a variety of test animals. Fetotoxic effects, however, have been well documented.

The effects of PCB's on the male reproductive system in animals or humans has not been adequately studied. PCB's have been detected in human semen,[32] but there have been no studies of semen quality in relation to PCB exposure in humans.

Biochemical Effects of PCB's

Enzyme Induction

The principal biochemical effect of PCB's is the stimulation and induction of certain enzyme systems. Enzyme induction occurs in both the microsomal monoxygenase or cytochrome P-450 system and the aryl hydrocarbon hydroxylase or cytochrome P-448 system, and it has been observed in both man and experimental animals. Induction is not restricted to the liver. It occurs in numerous other organs including kidney, adrenal, lung, gut, skin and testes.[9]

Enzyme induction has at least two implications for human health: (1) the occurrence of disease secondary to the increased metabolism of endogenous or exogenous substances, and (2) the interference with medical therapy due to increased metabolism of administered drugs.

PCB's are more potent enzyme inducers than phenobarbital, a drug that occasionally causes clinical problems due to its enzyme-inducing effects. While the effects of phenobarbital decline after administration ceases, enzyme induction from PCB's persists long after cessation of exposure.[33]

Porphyria

Although hepatic porphyria has been observed in laboratory animals exposed to PCB's,[9] porphyria has not been reported in humans with exposure to PCB's.

Other

A number of reports implicate PCB's as immunosuppressants in animals.[34] Endocrine effects have also been

observed including estrogenic (rat)[35] and antiandrogenic (birds) activity.[36] The effect of PCB exposure on immune and endocrine system function has not been carefully studied in humans, so the relevance of these animal observations to human health remains unknown. There is one cross-sectional study of occupational exposure to PCB's which will include analysis of serum hormone levels and urinary metabolites, but results have not yet been published (personal communication, A. Fischbein, MD, Department of Community Medicine, Mt Sinai School of Medicine, New York, 1980).

Carcinogenicity

Epidemiology

There is too little epidemiological evidence available yet to evaluate the potential of PCB's as human carcinogens. A follow-up study of the patients with *Yusho* through 1977 has reported 51 deaths (31 with cause of death confirmed) of the 1,665 identified victims. There were 11 deaths from neoplasms, or 35.4 percent of the total.[37] While this rate is higher than the 21.1 percent in the population of the same prefecture in 1977, these data were not age-adjusted. No particular site had increased incidence; and there were no deaths from malignant melanoma, a tumor previously suspected to be linked to PCB exposure.[38] Two instances of liver cancer and two of lung cancer were reported, but smoking and drinking patterns were not available.

A retrospective cohort mortality study of 2,567 workers in two capacitor manufacturing plants was recently completed by the National Institute of Occupational Safety and Health.[39] No statistically significant standardized mortality ratio for any cause of death among exposed workers was found. Deaths from liver cancer, cirrhosis of the liver and rectal cancer were slightly higher than expected, though these higher rates were not statistically significant and no information was available on medical histories, including drinking patterns. There was no relationship between increased mortality from all causes of cancer, rectal cancer or liver cancer and length of exposure to PCB's.

The observed lack of a statistical association between PCB exposure and cancer, could, however, be due to limitations in the study design. First, despite the large cohort, there was a relatively small number of deaths (163) reviewed, thereby severely limiting the statistical power of this study. Second, there were on the average only 15 years of follow-up for each exposed worker in the study, whereas latency periods of 20 to 30 years are not uncommon for cancer deaths. Third, environmental levels were quantified for 1977 only. There were no data on actual PCB exposures during the time when most of the population at risk was employed. Finally, more than 50 percent of the sample had exposure to PCB for only two years or less.

Two additional cohort mortality studies are underway. The first is a mortality survey of the entire work force employed between 1952 and 1957 at the largest United States facility that manufactured capacitors and transformers. There is detailed information available on exposure levels in the plant. While the duration from onset of exposure is shorter than optimal, the information will at least give data on the short-term mortality experience of a heavily exposed occupational group.[40]

The second is a similar occupational mortality study, also of workers exposed in capacitor and transformer manufacturing. More than 2,000 workers have been identified for this study but no further details are yet available.[41]

Animal Cancer Tests

Several PCB mixtures are clearly carcinogenic in a number of rodent bioassays, producing liver tumors (hepatocellular carcinomas).[42-44]

Because high doses of PCB's are known to cause extensive injury to liver tissue, it is important to consider the dose levels at which liver carcinomas were produced in the rodent bioassays. In two studies in rats, significant increases in hepatocellular carcinoma were present at doses that did not produce gross histologic changes. Hepatocytes were somewhat enlarged (probably due to microsomal enzyme induction), but no extensive fatty infiltration or necrosis occurred, as was characteristic of bioassays at higher dose levels.[44]

None of the PCB mixtures are active in short-term tests for mutagenicity, a finding that holds true for most heavily chlorinated carcinogens. However, substantial confirming evidence for carcinogenicity is provided by positive cell transformation assays using these same PCB mixtures.[45] Thus, under the proposed Occupational Safety and Health Administration (OSHA) criteria, PCB mixtures should be considered category I carcinogens.[46] Both the International Agency for Research on Cancer[4] and the Environmental Protection Agency[3] have concluded that based on available animal data, PCB's should be considered as potential human carcinogens.

Medical Surveillance and Biologic Monitoring

Medical surveillance and biologic monitoring are of limited usefulness in predicting health hazards if dose-response relationships are not known. This certainly is the case with PCB's. Based on animal toxicology, there are many *suspected* adverse effects of PCB's which might result from exposure in occupational or environmental settings, but very few have been documented well enough to give even rough estimates of "no-effect" or "safe" levels. A large percentage of nonoccupationally exposed people have detectable PCB levels in body fat, blood and milk. However, any attempt to estimate an adverse effect associated with increases above this background level necessarily involves extrapolation from much higher dose animal experiments and therefore is subject to considerable error, especially when the pronounced variation in sensitivity of various animal species is taken into account. Furthermore, not enough is known regarding the relative dose-response characteristics of the various documented effects (such as liver damage and skin changes) to state that in the absence of a particular sign, symptom or laboratory

abnormality, the risk of long-term effects (cancer, reproductive toxicity) will be negligible.

For a clinician confronted with a worker who has a history of exposure to PCB's, the approach to management cannot be easily outlined. Given the current analytic methodology, residues can be measured in blood or tissue in the parts per billion range and compared with background; but assigning a health risk to a given level is virtually impossible, especially given the lack of pharmacokinetic data. Often patients are being evaluated after a considerable lag period (years) since last exposure occurred and extrapolation to peak blood levels is not possible. In fact, it may be that residue levels bear little relationship to the health risk. For example, the lower chlorinated compounds may be more toxic, but they are more rapidly metabolized and excreted. Thus, they are less likely to persist in blood or fat. Further, with the possible exception of chloracne, the presence of specific signs, symptoms or laboratory abnormalities is very difficult to definitely relate to PCB exposure in any given patient.

Given these uncertainties and the potential for serious health effects, the approach to monitoring should emphasize environmental sampling. Every attempt should be made to minimize exposure by using engineering controls or personal protective measures in those occupations where exposure still occurs (for example, for utility repair workers). Biologic monitoring (such as PCB serum levels) may be used to assess the effectiveness of environmental control, but it is really best utilized within a specific research protocol and probably has little value in the routine work-up of individual patients.

To further illustrate the complexity of medical surveillance regarding PCB exposure, one question might be considered: What is a rational approach to monitoring utility workers or others with some potential for ongoing occupational exposure?

There is certainly no single correct approach. For example, four occupational health physicians on the advisory committee to Cal/OSHA (the state regulatory agency in charge of enforcing occupational health and safety regulations in California), all familiar with the toxicology literature on PCB's, found it extremely difficult to develop a definitive protocol. PCB serum levels, although probably the best indicator of exposure, are difficult to correlate with health risk and are too expensive ($100 per sample) to be used in large-scale screening examinations. History and physical examination would be useful in detecting cases of chloracne, but the absence of chloracne would not rule out significant exposure.

Liver function tests have two problems: They are very nonspecific, so that any abnormalities would have to be carefully evaluated (repeat testing, careful ethanol history and possibly PCB serum levels) before they could be related to PCB exposure. Normal values, on the other hand, would not rule out significant exposure because the endpoint of primary concern is not liver disease *per se* but the potential cancer risk from an increased body burden.

A practical approach would be to initiate one-time general screening of all workers with history of exposure including skin examination and baseline liver function tests. This would estimate the prevalence of skin and liver disease in the population and establish a baseline for each employee. Subsequent testing would be limited to employees with clinical problems or histories of extensive exposure—such as from an accidental spill or a capacitory rupture causing heavy skin contamination.

If a subset of workers (of sufficient sample size, approximately 25 or more) could be identified that were at highest risk of exposure (such as cleanup or maintenance crews), follow-up could be done at routine intervals with determinations of serum PCB levels. Results of PCB levels on such a subgroup would serve as a check on the adequacy of work practices and protective gear, and if elevated, they would serve to trigger further medical evaluation in the larger population.

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Medical Practice Questions

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Nuclear Magnetic Resonance

QUESTION:

Is nuclear magnetic resonance (NMR) considered an established medical practice tool or is it considered investigational?

OPINION:

In the opinion of the Scientific Advisory Panels on Nuclear Medicine and Radiology, Nuclear Magnetic Resonance (NMR) imaging is an investigational procedure at present. Several NMR imaging systems are under development and evaluation. Controlled investigations are required to determine the clinical utility of this promising diagnostic tool.

Only after large numbers of comparative studies between NMR imaging and other more conventional imaging modalities, such as computerized tomography (CT), radiography, ultrasonography and radionuclide imaging are done and statistically analyzed, can the true advantages and limitations of this technique be determined.

Specialty Conference

Metabolic Causes of Nephrolithiasis

Discussant
DONALD J. SHERRARD, MD

This discussion was selected from the weekly Grand Rounds in the Department of Medicine, University of Washington, Seattle. Taken from a transcription, it has been edited by Drs Paul G. Ramsey, Assistant Professor of Medicine, and Philip J. Fialkow, Professor of Medicine and Chairman of the Department of Medicine.

DONALD J. SHERRARD, MD:* Although advances in medical therapy make it possible to treat most patients who have nephrolithiasis, many physicians are unaware of newer therapeutic strategies. As a result, renal stones continue to plague their patients. In this discussion I review recent progress in defining the major metabolic abnormalities causing stones and outline an approach to the management of each disorder. Only metabolic causes of nephrolithiasis are considered here; the role of infection and obstruction in causing stones is not included.

Hypercalciuria

The stones most commonly found in the urinary tract are composed of calcium oxalate and may be caused by an excess of calcium, urate or oxalate in the urine (Table 1). Hypercalciuria, the most frequent of these disorders, is diagnosed when a 24-hour urine calcium content exceeds 300 mg in men or 250 mg in women. These threshold levels may be somewhat arbitrary, but values of 250 mg for men and 200 mg for women should be regarded as suggestive.[1] When determining timed urine calcium concentration, it is important to measure the creatinine level in the same urine specimen. Because creatinine is excreted at a constant rate (about 20 mg per kg per 24 hours), its measurement provides an internal check of the accuracy of the urine collection.

Hypercalciuria may result from increased gastrointestinal absorption of calcium, from renal tubular leaking of calcium or from excessive bone resorption as a result of hyperparathyroidism. Clinically, it is important to distinguish the cases of hyperparathyroidism from the others because they are treated differently from renal and absorptive cases of hypercalciuria, which are treated identically.[1,2] Patients who have excessive bone resorption due to hyperparathyroidism usually have hypercalcemia. Persistent "high normal" serum calcium levels may be seen, however, and should stimulate a physician to determine the level of parathyroid hormone in the blood.

Hypercalciuria due to excessive absorption of calcium from the gastrointestinal tract has been subdivided into fasting and nonfasting types,[3] a distinction that relates to the severity of the defect. Patients who have severe absorptive hypercalciuria excrete excess calcium even while fasting, presumably because of prior massive absorption. When a less severe disorder is present, patients have increased urine calcium content only in the postabsorptive state. Urine calcium level will exceed the upper limits of normal in both types if a 24-hour specimen is assayed, but absorptive hypercalciuria may not be detected if only an overnight specimen is used.[3]

Recently the role of 1,25-dihydroxyvitamin D_3 in increasing calcium absorption has been explored.[4,5] Parathyroid hormone is the trophic hormone for hydroxylation of 25-hydroxyvitamin D_3 to the active metabolite, 1,25-dihydroxyvitamin D_3.[6] It presumably mediates this activation by blocking phosphate entry into the renal tubular cell. In patients who have a renal tubular leak of phosphate, the resultant decrease in intracellular phosphate is thought to lead to an endogenous increase in 1,25-dihydroxyvitamin D_3 levels, which has been observed in these patients. The 1,25-dihydroxyvitamin D_3 levels are elevated to the point where they cause increased absorption of calcium from the gut (the primary target organ of 1,25-dihydroxyvitamin D_3). The increased calcium absorption suppresses parathyroid hormone secretion. Increased amounts of 1,25-

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TABLE 1.—*Metabolic Causes of Calcium Oxalate Stones*

- Hypercalciuria
  - Absorptive
  - Renal
  - Resorptive (hyperparathyroidism)
- Hyperuricosuria
- Hyperoxaluria
  - Oxalosis (increased production)
  - Enteric (increased absorption)
  - Absorptive (with normal bowel)
    - Oxalate precursor ingestion
      - Vitamin C
      - Ethylene glycol
    - Oxalate
      - Foods high in oxalate—spinach, rhubarb, leafy vegetables, oxalis, chocolate, tea
      - Possible low calcium intake
  - Pyridoxine deficiency

dihydroxyvitamin D_3 may also participate in the suppression of parathyroid hormone.[4] Enhanced calcium absorption from the gut leads to an increased filtered load of calcium, and the suppression of parathyroid hormone results in a decreased tubular reabsorption of calcium in these patients. The consequence of an increased filtered load and a lowered tubular reabsorption is hypercalciuria.

The mechanism underlying renal hypercalciuria is not known. Patients who have this disorder have renal tubular wasting of calcium and a resultant increase in parathyroid hormone levels (that is, a secondary form of hyperparathyroidism).[2] This increase in parathyroid hormone stimulates 1,25-dihydroxyvitamin D_3 production (a secondary hypervitaminosis D), which enhances calcium absorption in the bowel and resorption in the bone. Patients with renal hypercalciuria can be distinguished from those with absorptive hypercalciuria by a raised parathyroid hormone level. A normal serum calcium level helps to distinguish them from patients with primary hyperparathyroidism. If the serum calcium level is in the high normal range, however, this latter distinction may be difficult. Careful monitoring of treatment (see below) may be the best way to distinguish patients who have renal hypercalciuria from those who have primary hyperparathyroidism.

Thiazide diuretics are effective as primary treatment for hypercalciuria in the absence of primary hyperparathyroidism. These drugs increase both proximal and distal tubular reabsorption of calcium. The proximal effect, however, may be blunted in patients who ingest a large amount of sodium. Therefore, if they do not respond sufficiently to thiazides, the urine sodium level should be determined. For patients with excessive sodium in the urine, dietary sodium restriction may be necessary to maximize the benefits of thiazide treatment. The distal effect of thiazides requires the presence of parathyroid hormone,[7] but chlorthalidone, a diuretic similar to thiazides, appears to work even in the absence of parathyroid hormone and should be effective in hypoparathyroid patients.[8]

The response to thiazide treatment may be helpful in distinguishing renal hypercalciuria from hyperparathyroidism. In patients with renal hypercalciuria, thiazides reduce urine calcium excretion and produce only a transient rise in serum calcium level. In hyperparathyroid patients, however, persistent, often steadily worsening, hypercalcemia will be seen after thiazide therapy. Very close monitoring of a patient (that is, at least weekly) is essential if thiazide therapy is to be used diagnostically in this manner.

Occasionally patients with very severe hypercalciuria will not respond adequately to thiazides alone, even at maximal dosage. In these patients hypercalciuria may decrease by 50 percent and the urine still have excessive calcium. The addition of phosphate will benefit them. Phosphate is not useful as primary therapy because in many patients diarrhea develops at high doses. Phosphate administered at a dosage of 2 to 3 grams per day in conjunction with thiazides, however, will further reduce the urine calcium level, particularly in patients with hypercalciuria with raised 1,25-dihydroxyvitamin D_3 levels. Phosphate therapy has been shown to reduce elevated 1,25-dihydroxyvitamin D_3 levels and, presumably as a result, reduce calcium absorption.[5] Finally, as with all other causes of stones, increased fluid intake will dilute the urinary constituents and reduce the likelihood of nephrolithiasis.[9]

Hyperuricosuria

Hyperuricosuria is probably the second most frequent cause of calcium oxalate stones. It can be determined either with a 24-hour urine collection or with a single, initial morning voiding. The disadvantages of the 24-hour collection methods are the inexact way in which 24-hour urines are usually collected and the fact that a preservative must be added to prevent urate precipitation. A single morning urine collection, using creatinine and urate levels in both serum and urine to determine the excretion rate of uric acid, avoids these problems and may be more accurate.[10] If 24-hour collection is used, a value greater than 700 mg for women or 800 mg for men is considered abnormal. If a single collection is used, a simple formula to calculate urate excretion rate is: urine urate $\times$ serum creatinine $\div$ urine creatinine. A value greater than 0.6 should be considered high.[10]

In patients with hyperuricosuria, calcium oxalate stones are seen about four times as frequently as uric acid stones.[1-3] Among the hypotheses to explain how hyperuricosuria causes calcium oxalate stones are the following: (1) A small urate precipitate may form a nidus for calcium oxalate, (2) excess urate may be a catalyst for precipitation of calcium oxalate and (3) urate may bind various solubilizers of calcium salts. There is some evidence to support each of these hypotheses and, because they are not mutually exclusive, all may play a role.

Two mechanisms can explain hyperuricosuria. Some patients have a metabolic disorder in which they excrete

excessive amounts of urate (that is, uric acid overproducers). Others, however, appear to have increased uric acid production as a result of immoderate protein intake, so-called protein gluttons.[1] Therapy should be selected for patients according to the specific cause of their hyperuricosuria. For a patient who has an immoderate protein intake, dietary restriction can be effective in reducing uric acid excretion. Many patients, however, cannot alter their diet. For those persons, and for patients who endogenously produce excessive uric acid, administration of allopurinol is indicated. By inhibiting the enzyme xanthine oxidase, allopurinol impairs the conversion of hypoxanthine and xanthine to uric acid. Much less uric acid is then produced and the precursors are excreted in conjunction with urate. Although uric acid precursors may occasionally form stones,[11] allopurinol has been remarkably effective in preventing further stones in patients with hyperuricosuria.[1] Alkalization of the urine and increased fluid intake are also helpful, but may not be necessary.

Hypercalciuria and hyperuricosuria frequently coexist. In patients with recurrent stones, both urate and calcium excretion should be clearly defined. When hypercalciuria and hyperuricosuria are found, both require treatment.[1]

Hyperoxaluria

The rare metabolic disorder, oxalosis, has been recognized for many years as a cause of nephrolithiasis.[12] Normal excretion of oxalate is 45 mg a day or less. Children who have oxalosis frequently excrete more than 150 mg a day; renal insufficiency may develop in early infancy and the children die of renal failure by the age of 5. Some children survive into the teenage years, and a few patients have been referred for dialysis or transplantation. The latter therapy has frequently failed because of oxalate deposition in the transplanted kidney. Although prolonged survival has been reported with dialysis, oxalate deposits may damage vessels, bone and other tissues.[13]

More recently, patients with gastrointestinal disease have been found to have disorders of oxalate metabolism. "Enteric hyperoxaluria" seems paradoxical because patients who have malabsorption of essential nutrients hyperabsorb oxalate, a nonessential substance. The explanation is actually simple, however. With malabsorption, fat remains in the stool and binds available calcium. Normally the nonabsorbed calcium, which constitutes 70 percent of our diet, forms a precipitate with malabsorption, bile salts are poorly reabsorbed in who have steatorrhea, however, the available calcium is bound by fat and water-soluble oxalate is well absorbed. In addition, when there is ileal disease in association with malabsorption, bile salts are poorly reabsorbed in the distal small bowel. Bile salts stimulate oxalate absorption in the colon and in patients with ileal disease or an ileal bypass, oxalate absorption is further enhanced.[14]

The first step in treating enteric hyperoxaluria is to decrease fat intake, thereby reducing the severity of steatorrhea and allowing more calcium to be available for precipitation with oxalate. Second, adding calcium to the diet provides more ionized calcium in the bowel lumen. Third, avoiding foods high in oxalate, such as chocolate, rhubarb, spinach and tea, reduces the availability of dietary oxalate.[15] Finally, using an anion resin, such as cholestyramine, also reduces oxalate absorption. Although these measures significantly lower the absorption and urinary excretion of oxalate, urinary oxalate can remain above normal and stone formation may continue. In selected patients, other measures may be necessary, such as surgical correction of a gastrointestinal defect (for example, ileal bypass).[14]

With an improved oxalate assay, some patients who do not have gastrointestinal disease have been identified in whom oxalate is absorbed in excess from the diet.[16] Robertson and Peacock[17] have shown that excessive oxalate in the urine can be associated with renal stones in patients who have neither enteric hyperoxaluria nor oxalosis. The treatment of hyperabsorption of oxalate in these otherwise normal patients primarily involves avoidance of foods high in oxalate. Administering a low dose of an anion resin, reducing fat intake or increasing calcium intake may also be effective, as in patients with enteric hyperoxaluria.[14] Interestingly, thiazide diuretics[18] and allopurinol[19] reduce urine oxalate levels and part of the beneficial effect of these agents may be due to reduced oxalate excretion.

Another cause of hyperoxaluria and nephrolithiasis is excessive use of vitamin C. This substance is metabolized to oxalate and high doses of vitamin C lead to increased renal oxalate excretion.[20] Several patients recently seen in Seattle who have recurrent nephrolithiasis have had elevated urine oxalate levels that declined to normal with cessation of vitamin C use. In subsequent follow-up of these patients for 18 months, no further stone formation has been observed.

Pyridoxine deficiency, a cause of abnormal metabolism of carbohydrates, may also cause hyperoxaluria.[12] Correction of this deficiency reverses the abnormal oxalate production and excretion. The recognition of this problem has led to the use of pyridoxine in high doses to treat children with oxalosis. Some children respond to pyridoxine therapy with a reduction in urinary oxalate and an associated clinical improvement.

Massive oral oxalate intake may also cause hyperoxaluria. Whereas common foods—including chocolate, rhubarb, spinach and tea—contain modest amounts of oxalate, only enormous quantities of these foods are associated with hyperoxaluria. An important source of oxalate that may cause hyperoxaluria if ingested in small quantities is the plant oxalis, which grows in the back country of the western United States. Oxalis has a tangy, "interesting" flavor and is often picked by hikers to chew. Hikers and backpackers should recognize and avoid this plant. Oxalis looks like clover, though the leaves are two to four times larger. It grows close to the ground and the leaves have blunt ends

rather than the pointed end of a clover leaf. It has a small white flower that is usually seen in the spring.

Uric Acid Stones

About 5 percent of renal calculi are uric acid stones. They occur in patients who have hyperuricosuria[21] and in patients who have persistent aciduria.[22] Hyperuricosuria more frequently leads to calcium oxalate stones, as discussed earlier. In about 20 percent of the patients with hyperuricosuria, however, uric acid stones will develop. These stones are radiolucent and can be distinguished from calcium oxalate stones on roentgenograms. If x-ray studies are not done, a stone analysis will provide the diagnosis.

The clinical management of patients with hyperuricosuria is not affected by identification of the type of stone. The treatment for hyperuricosuria is the same, whether the stone is composed of urate or calcium oxalate. Patients who have hyperuricosuria are treated by reduction in protein intake and the use of allopurinol. Alkalization of the urine to enhance urate solubility and increased oral intake of fluids may be necessary for patients who do not respond to allopurinol administration.

Uric acid stones also occur in patients whose urine is persistently acidic.[22] This condition occurs most frequently in older persons when ammonia production is reduced. Decreased ammonia production by the kidney —a common consequence of aging—is associated with increased use of phosphate buffers to excrete hydrogen ions. Because the dissociation constant of the phosphate buffer system is 6.8, to excrete hydrogen ion using this buffer requires a urine pH consistently in the 5 range. Because uric acid is insoluble at low pH, uric acid stones will form. In addition, elderly patients often have a low fluid intake and urine volume may be low, causing a further reduction in urine pH and a higher urate concentration. Persistent aciduria should be strongly suspected in an older patient who passes a uric acid stone. The diagnosis can be confirmed by determining urine pH several times during a 24-hour period. Alkali administration is the primary treatment for persistent aciduria. In addition, oral fluid intake can be increased to tolerance and allopurinol can be added to reduce the uric acid load. It is not necessary, in these patients, to alkalize the urine constantly. Providing intermittent alkaline urine, as normally occurs, will usually be sufficient to prevent nephrolithiasis.

Cystinuria

Cystine stones are also radiolucent. Cystinuria (not to be confused with cystinosis) is an autosomal recessive disorder and results from failure of proximal tubular reabsorption of dibasic amino acids, including ornithine, arginine, lysine and cystine.[23] As the urine is concentrated in the distal tubule and collecting duct, cystine, the least soluble of the group, will frequently form a precipitate. When a patient with nephrolithiasis in the late teenage or early adult years has a family history of renal stones, cystinuria should be suspected and a urine sediment examined. Cystine crystals, which are regular hexagons, are not seen in normal urine and are diagnostic of the disorder. The diagnosis of cystinuria can be confirmed by analyzing a stone or measuring the urine cystine content.

Treatment of cystinuria may be accomplished with administration of fluids and alkali. If a patient does not respond to these measures, penicillamine administration may be indicated. Cystine is composed of two cysteine molecules united by a disulfide bond. Penicillamine can break the disulfide bond of cystine, forming a cysteine-penicillamine compound that is soluble. In those patients who do not experience side effects, penicillamine provides effective treatment. Because of a high incidence of severe side effects, however, penicillamine should be used only if fluids and alkali fail.

Renal Tubular Acidosis

In renal tubular acidosis, calcium is mobilized from bones and frequently deposited in the kidney, causing either stones or nephrocalcinosis and, ultimately, renal failure.[24] In proximal renal tubular acidosis, bone calcium is mobilized as a result of acidosis, but several substances that are poorly reabsorbed in the proximal tubule enhance the solubility of calcium salts. Stones are a rare complication of proximal renal tubular acidosis but are more frequently seen in distal renal tubular acidosis. When distal renal tubular acidosis is likely, a patient should be tested for systemic acidosis, as well as a urine pH above 5.6. If renal tubular acidosis is treated with alkali in sufficient quantities before the development of nephrocalcinosis or renal impairment, correction of the acidosis can prevent both nephrolithiasis and renal damage. Once the disorder is far advanced, however, therapy may be less effective.

Rare Causes of Nephrolithiasis

The disorders discussed thus far account for more than 95 percent of metabolic causes of renal stones. Extremely rare metabolic causes of nephrolithiasis include those due to xanthine, oxypurinol or other even less common substances that may form precipitates in the urine. Recently, triamterene has also been implicated in several episodes of nephrolithiasis.[25] The mechanism and frequency of triamterene-related nephrolithiasis are unknown. It is not worth pursuing investigation for these rare disorders unless the more common metabolic abnormalities have been ruled out by repeated testing.

Approach to a Patient With Nephrolithiasis

Many patients have only one kidney stone. It is the second stone, therefore, that should lead to a serious evaluation for metabolic abnormalities. Exceptions to this general policy might include patients under 25 years of age and women. Because stones are uncommon in both of these groups, investigation after a single episode of nephrolithiasis might be appropriate.

History and physical examination may not be helpful in the evaluation of nephrolithiasis. Stone analysis is

TABLE 2.—*Initial Evaluation of Patients With Recurrent Nephrolithiasis*

Laboratory Assays
Serum
Calcium (if high, measure parathyroid hormone level)
Uric acid
Creatinine
Bicarbonate (pH)
Urine
Calcium
Uric acid
Creatinine
Sodium
Oxalate (after calcium and uric acid)

TABLE 3.—*Evaluation of Uncommon Causes of Renal Stones*

Less Common Causes of Renal Stones and Method of Investigation
Cystinuria
Microscopic urine analysis: look for hexagon crystals
Determine urine cystine level
Renal tubular acidosis
Serum and urine pH
Acidosis of aging
Frequent urine pH determinations
Triamterene
History of use
Very rare causes
Urine xanthine study for xanthinuria
Urine oxypurinol study for oxypurinoluria

also rarely helpful because most stones are calcium oxalate. Another frequently used study that is usually of little benefit is the search for crystals in the urine. Calcium oxalate and urate crystals are frequently seen in normal urine and finding them in a patient with nephrolithiasis does not establish a diagnosis of the metabolic abnormality. The finding of a cystine crystal in the urine is important, however, because cystine crystals are never present normally.

Other laboratory studies are more helpful in establishing the cause of a kidney stone (Table 2). The serum calcium level should be measured more than once to evaluate the possibility of hyperparathyroidism. A serum urate level may be helpful if elevated, but hyperuricemia may not be associated with hyperuricosuria. Measuring the serum creatinine level is also helpful to determine if there is renal damage associated with nephrolithiasis.

Urinary measurements are the most helpful laboratory studies for evaluating a patient with nephrolithiasis. Because hypercalciuria or hyperuricosuria is associated with most renal stones, repeated measurements of urine calcium and urate should be done before other tests are pursued. Creatinine levels should always be measured simultaneously when timed urine specimens are obtained. If repeated (that is, at least three measurements) urine calcium and urate levels are normal, then urine oxalate levels should be determined. Oxalate is usually measured in a commercial laboratory at considerable expense. If urine oxalate levels are raised, a review of the patient's history for ingestion of vitamin C or foods high in oxalate should be done. After the common metabolic disorders have been excluded, it is appropriate to pursue less frequent causes of nephrolithiasis, such as cystinosis, renal tubular acidosis and aciduria of aging, and to consider chemical analysis of a stone (Table 3).

Recent advances in understanding the metabolic abnormalities that cause nephrolithiasis should lead to a specific diagnosis of the cause of renal stones in most patients. Appropriate treatment strategies can be developed when the metabolic abnormality has been identified. It should be only a rare patient for whom a diagnosis cannot be found and only a noncompliant patient for whom treatment will not be effective.

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Medical Staff Conference

New and Old Concepts in Sarcoidosis

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR SMITH:* *For this conference we present a case that has many unusual features of sarcoidosis and in which a diagnosis of pseudotumor cerebri was made. The presentation will be given by Dr Paul Ludmer and the discussion by Dr James K. Brown.*

Report of a Case

DR LUDMER:† The patient is a 30-year-old black woman who was seen because of headache, palpitations and near syncope. This was the first University of California, San Francisco (UCSF), admission for this young woman referred from Oakland (California) Hospital. She was in good health until 1978 when after having a cesarean section she felt palpitations with mild dizziness. Premature ventricular contractions were recorded and she was treated with procainamide hydrochloride for six months. She did well until December 1979, when she noted progressive shortness of breath. In January 1980 an x-ray film of the chest showed bilateral hilar adenopathy and diffuse interstitial lung disease. Transbronchial biopsy yielded a specimen of tissue that had features of sarcoidosis, and the patient was given 60 mg of prednisone a day for ten months, with complete resolution of her symptoms. In August 1980 she was readmitted to Oakland Hospital because of bigeminy and hypokalemia; the arrhythmia resolved with correction of the hypokalemia.

During early 1981, her prednisone dosage was slowly tapered to 20 mg a day, and fatigue, severe headaches and blurring of vision developed. Skin nodules also appeared, but a skin biopsy gave nonspecific findings. Her prednisone dosage was empirically increased again to 60 mg a day. Her headaches resolved and her skin lesions improved. In August 1981 she was admitted again to Oakland Hospital for recurrent dizziness. Results of her laboratory examinations were normal, and procainamide therapy was again started for treatment of ventricular ectopy. She did well until February 1982, when her prednisone dosage was decreased to 20 mg a day and she again noted severe headaches and blurring of vision. By June 1982, however, she had 45 minutes of palpitations with near syncope. In September 1982 the patient noted increased episodes of symptomatic palpitations. Her prednisone dosage was tapered at that time to 20 mg a day and again headaches resulted. She was admitted to Oakland Hospital because of papilledema and ventricular ectopy. Taking procainamide at that time worsened her arrhythmias and she had nonsustained ventricular tachycardia, not controlled with administration of quinidine sulfate. She was transferred to Moffitt Hospital at UCSF. At that time she gave no history of chest pain, shortness of breath, paroxysmal nocturnal dyspnea, orthopnea, edema, cough, arthralgias, weakness, fever, chills or any visual changes.

In the past she had had hyperthyroidism, hiatal hernia, duodenal ulcer and cesarean sections and had taken birth-control pills. At the time of admission her only medications were quinidine (300 mg four times a day) and prednisone (30 mg a day). She had no allergies and did not drink alcohol or smoke. Her family history was significant for hypertension and sarcoidosis, and review of her systems showed a weight gain of 54 kg (120 lb) during the preceding 18 months while taking the prednisone.

On physical examination she was noted to be an obese woman who was resting comfortably but who complained of severe headache and blurring of vision. Her vital signs were normal and she was afebrile. She weighed 116.6 kg (257 lb). Examination of her skin

*Lloyd H. Smith, Jr, MD, Professor and Chairman, Department of Medicine.

†Paul Ludmer, MD, third-year resident.

Refer to: Brown JK, Ludmer P: New and old concepts in sarcoidosis—Medical Staff Conference, University of California, San Francisco. West J Med 1983 Apr; 138:546-551.

showed patchy, hyperpigmented, raised papular lesions on the trunk, extremities and face. Examination of the eyes was significant for bilateral papilledema and arteriolar narrowing. She had a supple neck and no enlargement of the thyroid gland and no adenopathy. Her lungs were completely clear and on cardiovascular examination there was only a systolic flow murmur. Examination of her abdomen, back, extremities and genitourinary system showed no abnormalities. Results of the neurologic examination were normal, except for papilledema, as noted.

The following laboratory tests showed normal values: a complete blood count, urine analysis, complete chemistry panel and thyroid function tests. Chest roentgenograms and electrocardiograms showed no abnormalities, except for bigeminy and a prolonged QT interval.

The patient was admitted to the coronary care unit and was observed to have multiple runs of nonsustained ventricular tachycardia that were only partially controlled with administration of lidocaine hydrochloride. An electrophysiologic study showed no inducible ventricular tachycardia. Administering disopyramide phosphate and procainamide did not control her arrhythmias, but all ventricular ectopy disappeared after the patient was started on a regimen of propafenone, a new type I antiarrhythmic agent. Two-dimensional echocardiography and gallium scans showed no evidence of large collections of sarcoid granulomas in the heart, and lumbar puncture showed normal cerebrospinal fluid with no cells and an opening pressure of 460 mm of water. Results of computerized tomographic brain scanning were normal. She was thought to have pseudotumor cerebri, and administration of acetazolamide was begun. Her condition rapidly improved and she was discharged free of symptoms and on a regimen of propafenone, acetazolamide and prednisone (25 mg a day).

Discussion

DR BROWN:* The illness in this patient is quite typical of sarcoidosis in many ways. Her illness became apparent when she was in her late 20s; sarcoidosis is a disease of young adults. The illness occurred in a black patient; for uncertain reasons sarcoidosis seems to be about ten times as common in black as in white patients. A prominent symptom early in this patient's course was shortness of breath; according to a recent report of a large series from Los Angeles,[1] 49 percent of patients with sarcoidosis present with respiratory symptoms, 24 percent with systemic symptoms (for example, fever and weight loss), and 7 percent with symptoms attributable to focal extrathoracic disease, such as cutaneous, arthritic or ocular manifestations. Interestingly, 20 percent of cases of sarcoidosis are detected because of abnormalities found on chest roentgenograms that were done for incidental reasons.

A roentgenogram of the chest in this patient showed bilateral hilar adenopathy and diffuse infiltrates in the lung. These findings are typical radiographic manifestations of sarcoidosis, which have been divided into three stages. Radiographic stage I pulmonary sarcoidosis is bilateral hilar adenopathy with clear lung fields. Stage II sarcoidosis is bilateral hilar adenopathy associated with reticulonodular infiltration of the lung fields, and stage III shows parenchymal infiltration in the absence of hilar adenopathy. About 40 percent of all patients with newly diagnosed sarcoidosis will have radiographic stage I disease. In sarcoidosis the hilar adenopathy is nearly always bilateral and is often associated with right paratracheal adenopathy. In sarcoidosis the hilar adenopathy always precedes or coincides with the development of infiltrates. The opposite progression—that is, infiltrates followed by hilar adenopathy—should lead one to suspect disorders other than sarcoidosis, such as lymphoma, mycobacterial infection or fungal diseases.

A prominent characteristic of the illness in this patient was intracranial hypertension associated with headaches, blurred vision and papilledema. Rarely, in patients who have sarcoidosis, hydrocephalus and intracranial hypertension may develop because of focal granulomas in the central nervous system or because of full-blown granulomatous meningitis. The normal findings on computerized tomographic brain scan, however, and the lack of cells in the cerebrospinal fluid established that our patient had neither hydrocephalus nor meningitis. The most likely cause of the neurologic problems was pseudotumor cerebri related to withdrawal of prednisone.[2]

The etiology of sarcoidosis is not known. It has long been suspected that it is caused by a transmissible agent. Indeed, when sarcoid splenic or nodal homogenates were injected into the footpads of mice, granulomas developed 6 to 15 months after the injections.[3] These granulomas did not develop when the homogenates were irradiated or autoclaved before the injections. The identity of the presumed agent present in these homogenates has remained elusive. For many years it was suspected that *Mycobacterium tuberculosis* was the agent, but the many differences between sarcoidosis and tuberculosis make any etiologic association between these two conditions unlikely. Sarcoidosis often affects the eyes, salivary glands, skeletal muscle and myocardium, and these are all sites in which tuberculosis is exceedingly rare. Likewise, tuberculosis often affects the pleura, pericardium, peritoneum and adrenal gland—all sites in which involvement by sarcoidosis is exceedingly uncommon. Caseation of the granulomas is rare in sarcoidosis and commonly occurs in tuberculosis. In Great Britain, at least, sarcoidosis appears to affect equally patients from all socioeconomic levels, whereas tuberculosis is much more common in socially and economically disadvantaged persons. In Denmark, where very careful epidemiologic records have been kept for many decades, the prevalence of sarcoidosis has remained relatively constant over the past few

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decades despite a sharp decline in the rates of tuberculosis. Cutaneous anergy is a common finding in sarcoidosis and is rare in tuberculosis, except in those patients who have extensive disease. Antituberculous drugs have no effect on the course of sarcoidosis.

Although an agent of sarcoidosis has not been identified, some progress has been made in our understanding of the mechanisms by which granulomas form in the lungs of sarcoid patients. The noncaseating granuloma is the histologic hallmark of sarcoidosis. This follicle of cells is composed of a peripheral ring of lymphocytes that surrounds macrophages and their precursors, the monocytes. Epithelioid cells and giant cells, which are probably derived from the monocyte-macrophage line of cells, also are located within the perimeter of lymphocytes. An important ultrastructural characteristic of all these cells is that they contain abundant, rough endoplasmic reticulum and they are all capable of active synthesis.

The new evidence as to how these granulomas form in the lungs of sarcoid patients comes largely from work by Crystal and co-workers at the National Institutes of Health.[4] To sample the inflammatory cells and their secretory products from the lungs of sarcoid patients, this group of investigators has used the technique of bronchoalveolar lavage. Lavage was carried out by wedging a fiberoptic bronchoscope into a small bronchus, infusing 20- to 25-ml aliquots of saline into the distal small airways and alveoli and aspirating the cell-containing fluid back through the port in the bronchoscope. About 10 to 30 million cells can be harvested from the lungs of a single patient by this technique. The predominant cell isolated in normal subjects is the alveolar macrophage. Interestingly, in the series reported on by Hunninghake and colleagues, there was a striking increase in the percentage of the total cells that were lymphocytes, both in patients who had sarcoidosis and in those who had hypersensitivity pneumonitis.[4] About 90 percent of these lymphocytes were T-lymphocytes. By contrast, there were reduced numbers of T-lymphocytes in the bloodstream of these patients, and this lymphocytopenia may be one of the mechanisms by which anergy to cutaneously applied antigens develops in cases of sarcoidosis. There were also qualitative differences between the T-cells in the lungs and those in the circulation of sarcoid patients. Whereas the circulating T-cells were small and relatively quiescent, the T-cells in the lungs were "activated," that is, large and actively synthetic. Interestingly, one of the substances secreted by these activated lung T-cells was a chemotactic factor for monocytes.

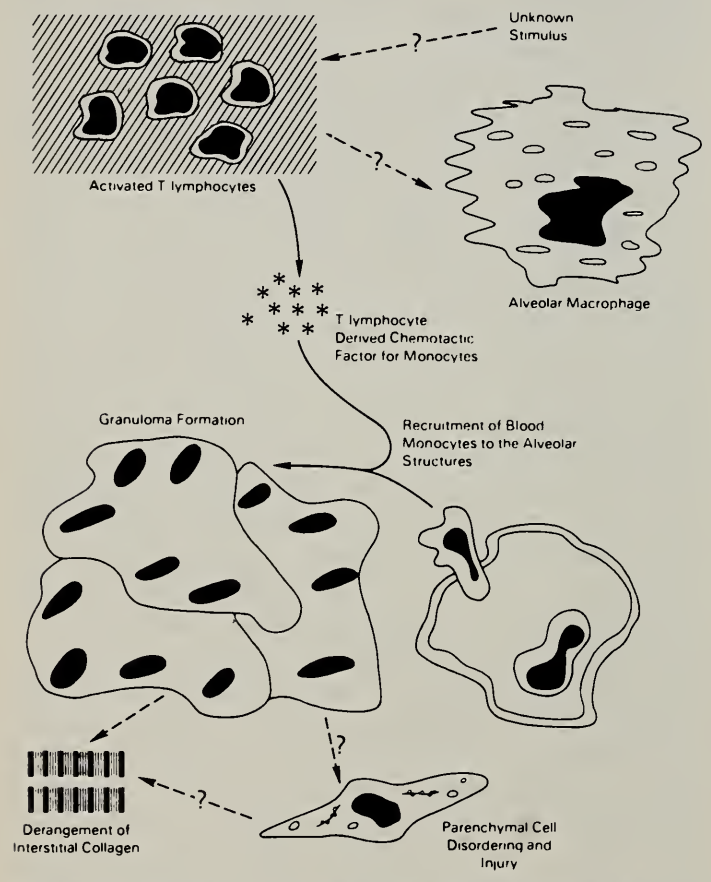

Figure 1.—Proposed pathogenetic sequence in the development of the granuloma in pulmonary sarcoidosis (from Hunninghake et al[4]).

Based in part on these observations, Hunninghake and associates proposed the following pathogenetic sequence in pulmonary sarcoidosis (Figure 1): Sarcoidosis begins with the inhalation of some agent into the lung. As in most cellular immune responses, the agent is probably processed in some way by macrophages that in turn cause the accumulation and activation of T-lymphocytes in the lung. A chemotactic factor for monocytes is released by the activated T-lymphocytes, and blood monocytes are recruited into the alveoli. Proliferation and differentiation of the monocytes lead to the development of the cellular constituents of the center of the granuloma, the epithelioid and giant cells.

Although this proposed sequence of events is a provocative one, its validity critically depends on the observed lymphocytosis in the fluid lavaged from the lungs of patients with sarcoidosis. Some investigators have found polymorphonuclear leukocytes, not lymphocytes, in the fluid lavaged from some patients who had sarcoidosis, particularly in those who had advanced lung disease.[5] This finding suggests that pathways other than the one outlined in Figure 1 may lead to the development of inflammation of the lung in pulmonary sarcoidosis.

Granulomas may bring about all of the manifestations of sarcoidosis by at least two different mechanisms: the simple mechanical effects of their physical bulk and the ectopic effects of substances secreted into the bloodstream by activated cells of the granuloma. No one knows if the pulmonary fibrosis that develops in some patients who have sarcoidosis is the result simply of irritative or mechanical effects of the granulomas in the lung or of some secreted substance that alters the

quantity or quality of the collagen in interstitial spaces to produce the fibrosis.

One group of extrapulmonary manifestations of this disease that may relate entirely to the mechanical effects of the granulomas is the cardiac manifestations. Granulomas are found in the myocardium of about 20 percent to 25 percent of all patients dying of sarcoidosis, but clinically significant cardiac complications occur in only about 1 percent to 2 percent of those who have active disease. Thus, the paroxysmal arrhythmias observed in the patient herein described were an unusual manifestation of this disease. The location of the granulomas in the myocardium correlates fairly well with the particular cardiac abnormality that develops in a patient. Presumably the fact that granulomas often form high in the interventricular septum accounts for the relatively high frequency of cardiac conduction disturbances, arrhythmias and sudden death in patients who have cardiac sarcoidosis. Left ventricular failure—or left ventricular aneurysm—develops when involvement of the left ventricular free wall is extensive. Very rarely involvement of the papillary muscle may cause mitral insufficiency in patients who have sarcoidosis.

Two other extrapulmonary features of this disease probably relate entirely to substances secreted by the granulomas. These are hypercalcemia and increased plasma concentrations of angiotensin-converting enzyme. In the small fraction of sarcoid patients who have hypercalcemia, it has been observed that the plasma concentrations of 25-hydroxycholecalciferol are within normal limits and concentrations of 1,25-dihydroxycholecalciferol (1,25-dihydroxyvitamin D_3) are increased. From these observations, one might conclude that the cause of hypercalcemia in sarcoidosis is an abnormality in the regulation of the 1-hydroxylase enzyme, which has been thought to be located in the kidney. Against this conclusion are data shown in Figure 2. These findings are sequential measurements that were made in a patient who had hypercalcemia and sarcoidosis.[6] At the time of the diagnosis of sarcoidosis, the patient's serum level of calcium was increased, as was the serum concentration of 1,25-dihydroxycholecalciferol. Institution of corticosteroid therapy reduced serum concentrations of both substances. Subsequently the patient underwent bilateral nephrectomy because of intercurrent renal disease. A few months later hypercalcemia developed, again accompanied by a high concentration of 1,25-dihydroxycholecalciferol. The institution of corticosteroid therapy resulted in a prompt reduction in concentrations of both 1,25-dihydroxycholecalciferol and calcium. The inescapable conclusion from these measurements was that 1,25-dihydroxycholecalciferol was being produced in some cell outside the kidneys. Conceivably, one of the inflammatory cells in the granuloma acquires the capacity to secrete this substance in some patients who have sarcoidosis. Alternatively, 1,25-dihydroxycholecalciferol normally may be synthesized in some extrarenal site,[7] and substances secreted by sarcoid granulomas may "derepress" normal regulatory mechanisms.

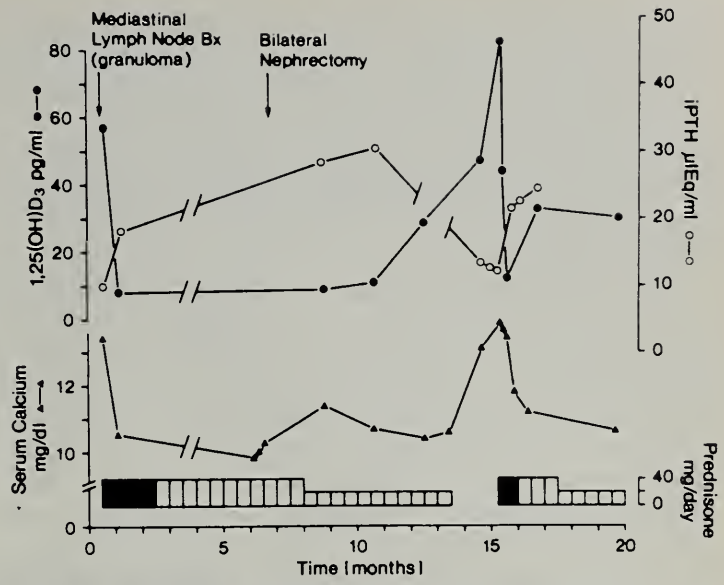

Figure 2.—Temporal relationships between serum concentrations of 1,25-dihydroxyvitamin D_3 (1,25[OH] D_3), immunoreactive parathyroid hormone (iPTH) and calcium to doses of prednisone administered in one patient with sarcoidosis. The solid portion of the bar representing the administration of prednisone indicates daily therapy, and the open portion indicates alternate-day therapy (from Barbour et al[6]).

About 80 percent of patients who have active sarcoidosis have high serum concentrations of angiotensin-converting enzyme, and the concentrations tend to fall with either spontaneous or glucocorticoid-induced remission of the disease. This enzyme is a dipeptide carboxypeptidase that is found normally in the endothelial cell of pulmonary capillaries. By immunocytochemical techniques, it has been established that very high concentrations of the enzyme occur in a sarcoid granuloma. Presumably, active synthesis of angiotensin-converting enzyme occurs in some cellular element of a granuloma, probably the macrophage or the epithelioid cell, to account for the elevated plasma concentrations observed in patients who have sarcoidosis. The alternate possibility—that the increased concentrations in the blood occur by another mechanism and that the enzyme is secondarily sequestered in a granuloma—has not been ruled out.

Although measurements of plasma concentrations of angiotensin-converting enzyme have proved useful diagnostically, the finding of increased concentrations occurs in conditions besides sarcoidosis. Those conditions in which there is a definite increase are Gaucher's disease, berylliosis and lepromatous leprosy. Those in which there is a probable increase include diabetes mellitus (especially juvenile-onset diabetes), hyperthyroidism, alcoholic liver disease and atypical mycobacterial infection. Relatively few patients with atypical mycobacterial infections have been studied. In the next few years it will be important to watch for the emergence of more information about the incidence of increased concentrations in patients who have active atypical mycobacterial infections, as well as other specific granulomatous conditions. Certain conditions that cause acute

injury to pulmonary capillary endothelial cells are capable, at least on theoretic grounds, of increasing serum concentrations of angiotensin-converting enzyme because the damaged cells may release the enzyme into the circulation. These conditions include adult respiratory distress syndrome, radiation damage to lungs and administration of some antineoplastic drugs, such as bleomycin sulfate.

Thus, although the finding of a raised plasma level of angiotensin-converting enzyme may suggest a diagnosis of sarcoidosis in a given patient, establishing the diagnosis definitively requires tissue biopsy, the finding of noncaseating granulomas in a tissue specimen and the exclusion of other specific causes of granulomatous disease by appropriate histochemical, microbiologic and serologic techniques. A number of procedures are available for obtaining tissue from patients who may have sarcoidosis. Of these, the most commonly used is the one carried out in our patient—fiberoptic bronchoscopy with transbronchial biopsy. When a bronchoscopist is able to obtain at least four adequate transbronchial biopsy specimens, granulomas will be found in specimens from 60 percent to 80 percent of sarcoid patients who have only hilar adenopathy on chest roentgenograms and 80 percent to 100 percent of those who have radiographically evident infiltration of the lung fields. The principal advantage of this test is that it does not require general anesthesia. A potential disadvantage is the small amount of tissue obtained, leaving open the disturbing possibility that tissue adjacent to that taken contained acid-fast bacilli or some other specific cause of the granuloma. Mediastinoscopy is another excellent procedure for establishing a diagnosis of sarcoidosis. Its chief advantage is the relatively large amount of tissue that may be obtained, making the likelihood of a missed diagnosis very small. The chief disadvantage is that it requires general anesthesia. Open lung biopsy is almost never required to establish this diagnosis. A biopsy of extrathoracic sites should be done when those sites are obviously involved clinically; that is, skin biopsy in those with infiltrative cutaneous lesions, epitrochlear or cervical lymph node biopsy when those nodes are obviously enlarged, liver biopsy when there is a clear-cut case of hepatitis and conjunctival biopsy in those with sicca syndrome in association with suspected sarcoidosis.

Having established a diagnosis of sarcoidosis, one is usually faced with the decision of whether or not to institute glucocorticoid therapy, as was the case in this patient. In evaluating any sarcoid patient for steroid therapy, one should be aware that this disease in most instances has a benign outcome even when no treatment is instituted. Of those sarcoid patients with only bilateral hilar adenopathy seen on chest roentgenograms at the time of diagnosis, 75 percent will have complete remission in two years. Of those with radiographically noted infiltration of the lungs, 50 percent will have remission in two years and 50 percent will have persistent infiltrates. Of the 50 percent with persistent infiltrates, in only about a third will full-blown pulmonary fibrosis develop. These statistics are derived from a study in which no glucocorticoid therapy was used.[8] Thus, even without treatment, the disease has a benign outcome in most instances. It is estimated that of all patients diagnosed as having pulmonary sarcoidosis in this country now, only 10 percent or 15 percent will have progression of their condition to pulmonary fibrosis.

On theoretic grounds, there are two reasons for intervening with glucocorticoid therapy in patients who have pulmonary sarcoidosis. First, if steroids relieved the respiratory symptom of dyspnea, which frequently develops in these patients, then such a development would be an adequate reason for administering this agent. Indeed, many sarcoid patients do experience relief of dyspnea on receiving corticosteroid therapy, as the patient described here did, as well as improvement in more objective indices such as chest roentgenograms and pulmonary function tests. Dyspnea is thus a clear indication for instituting glucocorticoid therapy in patients who have sarcoidosis. Second, if we knew that the early use of glucocorticoids in all patients who have sarcoidosis would prevent pulmonary fibrosis, the dreaded pulmonary complication of this disease, from occasionally developing, then perhaps it would be reasonable to recommend that all patients receive a course of glucocorticoids early in their disease. Unfortunately, it is not known at this time if steroid therapy prevents the development of pulmonary fibrosis. One can imagine the difficulty of the design of an adequate, randomized, large-scale study to test the long-term protective effects of steroids on pulmonary function. Such a study would require giving high doses of steroids to large numbers of sarcoid patients, most of whom would improve even without therapy. It would also require withholding therapy from some relatively sick patients, many of whom would improve on receiving the therapy. To summarize, there is a considerable amount of experience that suggests that some patients who have pulmonary sarcoidosis improve immediately with the administration of steroids. It is not known if the use of these agents prevents the development of pulmonary fibrosis in some patients.

Based on these considerations, one can make the following recommendations for the use of steroids in patients with pulmonary sarcoidosis: Any patient who has pulmonary sarcoidosis and dyspnea should be treated. A patient with radiographic evidence of pulmonary infiltrates but without dyspnea should be observed carefully. If there is significant radiographic or physiologic deterioration, then strong consideration should be given to institution of glucocorticoid therapy because such a patient is probably at relatively high risk for pulmonary fibrosis developing.

Summary

I have mentioned a few of the new concepts of sarcoidosis, particularly those related to the pathogenesis

of sarcoid granulomas and the possible importance of secretory products released from a granuloma in the production of some of the manifestations of this disease. I have also emphasized an old concept, the continued requirement for tissue biopsy to establish the diagnosis of this condition.

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Medical Practice Questions

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

CT Scans of Lumbar Spine?

QUESTION:

What are the indications for computerized tomography (CT) scans of the lumbar spine?

OPINION:

In the unanimous opinion of the Scientific Advisory Panels on Neurology, Neurosurgery and Radiology, computerized tomography (CT) of the lumbar spine is established medical practice. As a general principle, CT scanning of the lumbar spine is justified when there is a reasonable suspicion of clinically significant disease. This would include a number of disorders of congenital, traumatic, neoplastic and degenerative diseases affecting the spinovertebral axis, both on an intraaxial and extraaxial basis. Neurological, neurosurgical or orthopedic consultation is recommended before initiating a CT scan for such disorders. The frequency of serial scanning should be controlled by proper utilization guidelines. Under no circumstances should CT scanning of the lumbar spine be considered a screening procedure.

The CT scan often supplements and, in some cases, may eliminate the need for myelography. CT study of the lumbar spine, alone or in combination with metrizamide, can provide useful information that may not be available from plain myelographic studies. In many instances, both procedures may be indicated, since each provides a somewhat different perspective of spinal pathology. The efficacy of computerized tomography of the lumbar spine presumes the availability of adequate equipment and a procedural protocol.

Computerized tomography has become an effective, noninvasive diagnostic tool in evaluating disorders of the lumbar spine, and its usefulness will continue to increase.

Epitomes

Important Advances in Clinical Medicine

Urology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in urology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers or scholars to stay abreast of these items of progress in urology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Urology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities, California Medical Association, 731 Market St, San Francisco, CA 94103

Physical and Psychological Results of Penile Prostheses

PENILE PROSTHETIC insertion procedure has become a common treatment of both organic and functional impotence in men. Schoenberg and co-workers and Marshall and colleagues assessed the social, sexual and psychologic status of patients a year or more after implantation of one type of penile prosthesis (semirigid rod). An extensive and comprehensive questionnaire was sent to 90 randomly selected patients. In all, 49 questionnaires were returned and analyzed by computer. Of those patients who responded, 68 percent rated their postoperative emotional adjustment excellent or good, whereas 20 percent considered their adjustment to be less than adequate. One of the criticisms of the semirigid rod prosthesis is that a quasierect penis is difficult to wear comfortably and unobtrusively, but general activity and participation in sports remained about the same. Only 4 percent of the patients indicated embarrassment in public showers but 18 percent avoided public locker rooms and showers. Overall, 78 percent of patients were completely or somewhat satisfied, whereas 22 percent were rather or completely dissatisfied. Interestingly, 84 percent of the patients who had psychologic impotence were satisfied.

Patients who have functional impotence may be more motivated and "desperate" than the older population in whom impotence resulted from disease or surgical procedures. Because of insufficient numbers and the lack of partner participation in the decision to have the operation and in the appraisal of the results, no statistical conclusions could be drawn. Some of the exaggerated benefits claimed for the penile prosthesis may prove to be invalid when large numbers of patients are surveyed with detailed psychologic inventories.

JOSEPH J. KAUFMAN, MD

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Schoenberg HW, Zarins CK, Segraves RT: Analysis of 122 unselected impotent men subjected to multidisciplinary evaluation. J Urol 1982 Mar; 127:445-447

Finney-Flexirod Penile Prosthesis

THE TREATMENT of impotence by the use of a semirigid silicone prosthesis is firmly established. All current double-rod penile implants provide satisfactory coitus and improvements have been mainly directed toward providing more adequate concealment of a permanently rigid penis.

The Finney-Flexirod penile implant has three notable features not found in other designs. The distal tip is tapered to more nearly conform to the tapered tip of a distal corpus. Blunt-tipped implants cause the glans to have a ball-and-socket motion and can produce a so-called SST deformity (the glans falling ventrally). The tapered tip prevents this. This implant has a soft hinged segment that is positioned at the base of the penis to allow it to hang more freely in a dependent position, thereby allowing better concealment. The third improvement in this implant consists of a segmented proximal end that may be trimmed at the time of the operation for a proper fit. The total length of the corpus cavernosum cannot be determined accurately before the surgical procedure and this trimmable tail allows individual fitting. A penis is measured in a

stretched position from the mid glans to the pubis before operation and only this length implant need be used. This unique feature obviates the need for a full set of different-length implants, as is required with all other designs.

The most satisfactory route for implantation is through a penile-scrotal incision. This incision has the advantage of producing less postoperative edema than the previously used dorsal incision. So far we have implanted 432 Finney-Flexirod prostheses, with a success rate of 97 percent. Postoperative infection occurs in less than 1 percent of nondiabetic patients and 5 percent who have this disease. Prolonged postoperative pain very rarely occurs unless an implant that is too long for the corpus is used. Most patients and their partners are satisfied with the prosthesis and failure of the implant itself has never been reported. Additional improvements are being tested. ROY P. FINNEY, MD

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In Vitro Chemosensitivity of Human Bladder Cancer

URINARY BLADDER TUMOR specimens are obtained by endoscopic "cold-cup" biopsy. The specimens are divided into equal parts so that three or more drugs may be tested using a control set-up. In vitro chemosensitivity testing of human bladder cancer specimens has been done with thiotepa, mitomycin C, doxorubicin hydrochloride and cisplatin using a liquid culture medium.

A novel dye-exclusion assay, developed by Weisenthal and Marsden, used a liquid culture following drug exposure, then Fast Green staining with hematoxylin and eosin counterstaining of cells. The advantages of this new technique over the clonogenic assay are as follows:

- The liquid culture needs about 50,000 cells per assay instead of up to 1.5 million cells for a clone to develop.
- Results are obtained in three to five days compared with 14 to 21 days with the clonogenic technique.
- Simultaneous testing of three to four drugs with control culture could be set up with tumor specimens of about 1 million cells.
- A sensitivity report is available in time for instituting early treatment intravesically.

The overall success rate with this assay is 92 percent, with tumor sensitivity to doxorubicin highest, then mitomycin C, cisplatin and thiotepa in descending order. One observation made was that intrinsic chemosensitivity (cytotoxicity) of cancer cells may be the most important determinant of clinical response to intravesically given chemotherapy with thiotepa, whereas drug pharmacokinetics determine response to intravesical administration of doxorubicin. The in vitro chemosensitivity assay is now technically feasible for clinical use. A. O'TAYO LALUDE, MD

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Urodynamic Evaluation in Normal Children

WITH THE RECENT EXPLOSION of urodynamic technology, urodynamic evaluation in children is being done quite often. The indications for measuring urinary flow rate, sphincter electromyographic activity, urethral pressure profile and cystometrography, however, appear to vary from institution to institution.

In the treatment of children, our general approach is to limit invasive procedures to a minimum. Children present with three general classes of symptoms that suggest a possible urodynamic disorder: (1) an abnormal pattern of voiding, that is, abnormal act of voiding, voiding interval or urinary control, (2) recurrent infection and (3) unrecognized constipation. Although children with these complaints may compose a large proportion of a urologist's practice, not all of these children merit a full-scale urodynamic investigation. The need for any urodynamic investigation should rely on a detailed history, examination of the genitalia and observation of a urinary stream.

In children who have primary diurnal and nocturnal enuresis, there may be a history of neonatal complications, jaundice, colic of infancy or constipation. If a urinary stream is observed to be full, I would not do urodynamic testing but would formulate a tentative diagnosis of primary enuresis. Such children are treated with administration of oxybutynin chloride for day wetting or imipramine hydrochloride given at bedtime for night wetting. Stool softeners are prescribed if there is constipation. Fluid restriction after dinner is encouraged. A detailed history will help elicit a diagnosis of food allergies that may exacerbate enuresis. Children who do not respond to this empiric therapy should have radiographic evaluation and urodynamic testing.

Children may present with recurrent urinary tract infection. A urodynamic abnormality is suspected if there is a clear history of infrequent urination or an abnormal voiding pattern even with sterile urine. To record the actual voiding interval, a child's family should maintain a home diary. Infrequent urination suggests a presumptive diagnosis of vesical dyssynergia. Electromyography may be used in this instance to support a clinical diagnosis. Biofeedback or diazepam may be used to treat sphincter dyssynergia.

Because constipation may be an associated factor in many children who are seen for urologic evaluation, a specific history of this condition should be solicited.

Failure to detect an impaction may prevent successful pharmacotherapy of a voiding disorder. Peri-Colace is an effective stool softener and colonic stimulant.

When this empiric approach to abnormalities of urination is ineffective, excretory urography, voiding cystourethrography and cystoscopy should be done to exclude anatomic abnormalities. Measurement of the bladder capacity during these investigations is useful. Cystometrography may be done without added difficulty during nuclear cystography. These studies are carried out with routine urologic armamentarium. They do not require sophisticated urodynamic expertise. Urodynamic measurement of flow rates and sphincter electromyography or urethral pressure profile should be done when this conventional testing fails to provide a diagnosis adequate to direct specific therapy.

MAX MAIZELS, MD

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Prostatic Acid Phosphatase Is Not a Screening Test for Early Prostatic Cancer

THERE IS CONTROVERSY concerning the use of radioimmunoassays for prostatic acid phosphatase as a screening test for early prostatic cancer. In a prospective study conducted at Barnes Hospital, St Louis, acid phosphatase was assayed routinely by radioimmunoassay and an enzymatic method (thymolphthalein monophosphate substrate) in 285 patients admitted to the urologic service. There were raised levels of prostatic acid phosphatase in 16 patients (mean age 72.2 years) who had no clinical evidence of prostatic cancer, but all of whom had benign prostatic hypertrophy with bladder outlet obstructive symptoms requiring prostatectomy (5 by open abdominal operation, 11 by transurethral resection). Of these 16 patients, 6 also had an elevated serum acid phosphatase value by the enzymatic method.

Routine pathology examination of tissue sections failed to show carcinoma in any of the 16 specimens. During a median of 11 months follow-up, in no patient has clinical evidence of prostatic cancer developed (two died of unrelated myocardial infarctions). Six patients were available for postoperative acid phosphatase measurements and all values were normal.

We conclude that prostatic acid phosphatase determination by radioimmunoassay is not a useful screening test for early prostatic carcinoma. The futility of using the prostatic acid phosphatase level as a screening test in patients with clinically evident benign prostatic hypertrophy is also shown in our previously published report (Fair and co-workers). In that study, which included patients from all our hospitals, 349 patients with clinically evident benign prostatic hypertrophy had subsequent histologic examination of the prostate, 16 (6 percent) had occult prostatic cancer and only one of these (6 percent) had an elevated prostatic acid phosphatase level. In that same patient group, 24 who had histologically proved benign prostatic hypertrophy had elevated prostatic acid phosphatase levels. Thus, in this group of patients, benign prostatic hypertrophy was the cause of an increased prostatic acid phosphatase 24 times more often than stage A prostatic cancer.

WILLIAM J. CATALONA, MD

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Short-Course Chemotherapy for Genitourinary Tuberculosis

THE WIDESPREAD ACCEPTANCE of a new theory of short-course chemotherapy for pulmonary and genitourinary forms of the disease has been a major advance in tuberculosis therapy in the past few years. The worldwide impact of this breakthrough should be considerable in terms of improved patient compliance, lowered costs, decreased potential drug toxicity and more effective administration of treatment.

Physicians have long struggled with the chemotherapeutic regimen for tuberculosis in an attempt to shorten and simplify its course, but they were continually confronted with treatment failures and relapses. The previously accepted treatment for genitourinary tuberculosis consisted of triple-drug chemotherapy administered daily for a minimum of two years. The drugs for this regimen, both bacteriostatic and bactericidal, were selected mainly with the hope of preventing the emergence of drug-resistant bacilli in the long term. Now, however, in short-course chemotherapy combinations of more aggressive bactericidal drugs are selected because of their rapid and profound sterilizing activity. The drugs used (rifampin, pyrazinamide and, to a lesser extent, isoniazid and streptomycin sulfate) are all immensely bactericidal. Short-course chemotherapy thus uses a new rationale of therapy rather than merely giving formerly accepted regimens for shorter periods of time.

Through studies in various countries, regimens of six to nine months have been found to yield relapse-free rates of nearly 100 percent. There is no scientific evidence that therapy beyond nine months reduces the relapse rates. Though most of the trials were done in cases of pulmonary tuberculosis, two groups of investigators have led the research in genitourinary tuberculosis. Gow from England recommends giving a six-month course of chemotherapy for genitourinary tuberculosis, consisting of rifampin (450 mg), isoniazid (300 mg) and pyrazinamide (1 gram) daily for two months, followed by rifampin (600 mg) and isoniazid (600 mg) three times a week for another four months.

Dutt and Stead from the United States recommend a regimen consisting of rifampin (600 mg) and isoniazid (300 mg) given daily for about two months, followed by rifampin (600 mg) and isoniazid 15 mg per kg of body weight) daily or twice a week (depending on patient reliability) for another seven months. They add ethambutol hydrochloride (15 mg per kg) during the first two months if a patient has shown high initial drug resistance.

Many centers now recommend without reservation short-course chemotherapy for the initial treatment of genitourinary tuberculosis. The results may be even better than in pulmonary tuberculosis because fewer bacilli are usually found in renal lesions and rifampin is highly concentrated in the urine.

STUART D. BOYD, MD

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Single-Dose Therapy for Lower Urinary Tract Infection

ACUTE CYSTITIS is one of the two most frequent indications for administering antimicrobial therapy in adult women. Recent studies have shown that in nonpregnant adult women single-dose antimicrobial therapy may be as effective as conventional 7- to 14-day regimens.

Controlled trials have shown that amoxicillin trihydrate, sulfisoxazole and trimethoprim-sulfamethoxazole are effective when given in single-dose regimens in this population. In contrast, cephaloridine, cefaclor and cephalexin monohydrate have been shown to be poor choices. Caution should be exercised in extrapolating data to other agents without appropriate clinical evaluation. Likewise, single-dose regimens have been less effective than conventional treatment in pregnant women and children and should not be used in these patients.

Potential benefits of single-dose therapy include reduced medication costs, improved patient compliance with drug regimens, fewer side effects and a reduction in the rate of emergence of resistant bacteria. Additionally, the failure of a single-dose regimen to eradicate bacteriuria (when the organism is sensitive) may indicate more invasive infections and, some suggest, a need for closer follow-up and more extensive investigation to identify structural or functional abnormalities of the urinary tract. Careful bacteriologic follow-up evaluation should be done irrespective of the duration of therapy.

Although information regarding optimal choice and dose of an antimicrobial agent for single-dose treatment remains to be refined, oral amoxicillin (2.0 grams), sulfisoxazole (1.0 grams) or trimethoprim-sulfamethoxazole (160 and 800 mg, respectively) appear to be rational choices.

Administration of single-dose antibiotic drugs for lower urinary tract infection is safe and effective therapy for nonpregnant adult women.

PAUL F. SOUNEY

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Hospital Admission Rates in Men Who Have Had Vasectomies

FEARS based on findings from studies in animals about the long-term health of men who have had vasectomies have not been borne out in a large follow-up study. Using the records of a large health maintenance organization, the incidence of first hospital admission after vasectomy in 6,092 men (20,491 man-years of follow-up) was evaluated. Hospital admissions for various classes of disease and for a variety of specific illnesses were compared with the rates in members of the same health maintenance organization who had not had vasectomies. There was no evidence of an increased prevalence of arteriosclerotic disease in the men who had had vasectomies, the principal concern raised by the experiments in animals. The highest standardized rate ratio (vasectomized to nonvasectomized) for first hospital admissions was for diseases of the genitourinary system, whose diagnosis may have been prompted by the vasectomy.

These findings were further evaluated according to time since the vasectomy because it was assumed that hospital admittance causally associated with vasectomy would either increase or decrease in frequency in some regular fashion with time. No specific disease entity followed this pattern, with the exception of hospital admissions for mental disorders, which were less frequent in men who had had vasectomies than in men who had not and continued to decline with time after the vasectomy procedure.

ALEXANDER M. WALKER, MD, DrPH

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Walker AM, Jick H, Hunter JR, et al: Vasectomy and non-fatal myocardial infarction. Lancet 1981 Jan 3; 1(8210):13-15

Computerized Tomography, Lymphangiography and Gleason Scores for Staging Prostatic Adenocarcinoma

IT HAS BEEN well documented that the prognosis and metastatic progression of disease in patients who have adenocarcinoma of the prostate is determined by the presence or absence of pelvic lymph node metastasis. There is no information that supports an increased survival with either pelvic lymph node dissection or pelvic lymph node irradiation. The accurate preopera-

tive classification of patients who have or do not have positive lymph node involvement is therefore indicated to determine the aggressiveness of therapy and avoid unnecessary surgical procedures and irradiation.

The usefulness and accuracy of computerized tomography, lymphangiography and Gleason categories were evaluated in 53 patients who had clinical stage A, B or small C lesions. All 53 patients were candidates for interstitial irradiation and had had staging lymphadenectomy. Of the total of 53 patients, 50 had lymphangiography, 23 computerized tomographic scanning and 48 had Gleason scores assigned. The accuracy of lymphangiography was 58 percent, with a 12 percent false-positive and a 30 percent false-negative rate. The accuracy of computerized tomography in this series is 50 percent, with a false-positive rate of 14 percent and a false-negative rate of 36 percent. Correlation of Gleason scores shows no lymph node metastasis with Gleason scores of 5 and 6, 37.5 percent with scores of 7, 36 percent with scores of 8, 63.7 percent with scores of 9 and 100 percent with scores of 10. Combining computerized tomography and lymphangiography or lymphangiography and Gleason scores did not significantly increase the staging accuracy.

These findings confirm those of Benson and coworkers and Kramer and associates that show the inaccuracy of lymphangiography and computerized tomographic scanning and support the reliability of Gleason scores for preoperative staging.

In conclusion, lymphangiography and computerized tomographic scanning are not consistently accurate in preoperative staging and should not be routinely used. Gleason categorization is more accurate and reliable than lymphangiography or computerized tomographic scanning alone or in combination. Routine staging lymphadenectomy can be avoided in patients who have Gleason scores below 5 and in patients above 9. Intermediate groups with scores of 7 and 8 need lymphadenectomy to document pelvic node disease. Aggressive therapy should be considered in patients who have Gleason scores 2 through 8.

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Editorials

Polychlorinated Biphenyls Revisited

Dr Gideon Letz in this issue presents a summary of the toxicology of polychlorinated biphenyls (PCB's) for clinicians. This overview illustrates the usual dilemma we find ourselves in. The animal data suggest that PCB's affect the immune response and are fetotoxic and carcinogenic. In humans they have been shown to cause chloracne, and they may affect serum lipid levels and liver function, but, thus far, the possible effects on the immune system and on reproduction have not really been studied. Our attempts to determine whether these chemicals produce cancer in humans have, at best, been inadequate, but our dilemma goes even further.

In the first half of this century, not much attention was paid to chronic toxicity. If a chemical such as PCB had almost no acute toxicity, it was considered safe. It was not until Jensen, in 1966 in Sweden, found PCB's in the environment and then the first *Yusho* outbreak in 1968 that concerns about PCB's were voiced.

These chemicals were found to have spread extensively through the environment in the United States and other parts of the industrialized world. They were present in some of our foods, particularly fish, but also in cereal, eggs, poultry, meat and milk. How did they get there? Industry was not very careful in containing PCB's, which, in turn, led to contamination of rivers and lakes and, thus, fish. In the 1960s, PCB's were used in carbonless copying paper which was recycled and made into cereal boxes. The PCB's then migrated from the cereal boxes into the cereal. PCB's had many open-ended uses—for example, as additives in paints used on silos and as heat exchangers in feed processing operations. Through this use animal feed became contaminated. Such open-ended uses were discontinued in 1971 in the United States, and after the Toxic Substances Act was passed in 1976, the use of PCB's elsewhere has been gradually phased out. But, as the author points out, about half of the PCB's ever made are still in transformers and capacitors, and they continue to present an enormous management and disposal problem.

In addition to the environmental contamination, the general population was found to have body burdens of PCB's. Since PCB's are lipid soluble, they are primarily stored in adipose tissue. To a lesser extent, they are present in serum and some organs. They are also excreted in human milk. It is not known whether trace amounts of these chemicals at concentrations of a few milligrams per kilogram in adipose tissue or of a few nanograms per milliliter in serum have any impact on human health.

In the past, it has always been assumed that with exposure being constant a steady state is eventually reached where intake and excretion go into a balance and PCB's no longer build up in tissues. Since some of the PCB isomers are extremely persistent with a very long biological half-life, it is not clear whether or when this steady state would ever be reached during the average life span of the human being. It is now also apparent that some isomers in this PCB mixture are much more persistent and toxic than others, and it seems that the more toxic isomers are relatively bioconcentrated in the environment. Thus, PCB's that have passed through the environment may not be the same PCB's to which workers are exposed.

Once toxic effects have been observed in animals, the health of workers exposed to similar chemicals is usually reviewed. If these workers are found to be healthy, the animal data are immediately questioned. Perhaps we should first examine to what extent the human data are adequate and useful. As Dr Letz points out, too few workers have been examined, and their length of exposure has been too short to address the question of carcinogenic properties of PCB's. Furthermore, workers are exposed to the original commercial mixture, but the general population is exposed to a possibly more toxic mixture that has been modified by the environment. In addition, older workers have not been exposed to these chemicals during their childhood and in utero, but the younger members of the general population have been so exposed.

Because these chemicals are extremely persistent and because they do have chronic toxic effects in animals and are carcinogenic in rodents, it is only prudent to reduce human exposure to them as much as possible. It would not be in the interest of public health to wait for the carcinogenic or reproductive effects to be shown in humans. Once that point is reached, it would be too late to take preventive measures. It may not be possible to determine in individual cases whether PCB exposure has resulted in health effects, since such effects, with the exception of chloracne, are nonspecific. But, as Dr Letz points out, that should not deter us from seeking to reduce exposure to these agents.

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Medicine in a Forest of Thickets and Trees

In many ways physicians, and indeed the medical profession as a group, seem to be trying to find their way through what might be compared to a rather dense forest with many formidable trees. Moreover the forest is also full of thickets. The thickets are the administrative and bureaucratic frustrations in a physician's daily practice; in a different dimension, they often impede

or thwart organizational goals of the profession in behalf of patients and the public. The trees are the larger and more generic problems with which both practitioners and the profession as a whole must deal. They include such troublesome things as the endless rules and regulations imposed by often well-intentioned but poorly constructed laws, rising health care costs that no one wants any longer to pay, confusing signals about competition in medical practice and patient care, new kinds of relatively untried health care and practice plans that may or may not contain booby traps for physicians or their patients, many kinds of expensive and often wasteful litigation that seem to benefit lawyers more than anyone else—only to mention a few. It is easy for physicians and the profession to feel confused, frustrated and powerless while trying to find a path through a forest of thickets and trees such as these.

But in this forest other powerful forces are at work. It is clear that irreversible changes are taking place in health care. The force that drives these changes is progress in medical science and technology. The social, economic, political and human impact of this progress is unprecedented and has created new kinds of problems with which we do not yet know how to deal. Society wants access to the best of health care and, yes, health for all. The sophisticated health care personnel, equipment and facilities needed for this are proving to be overwhelmingly costly. Yet health and health care are national goals strongly supported by the public and this is important politically. And advancing medical science and technology have given rise to an array of ethical and legal issues that have important but as yet unresolved social, economic and political ramifications. It is more and more apparent that a genuinely new technologic, social, economic, political and even human interdependence may be emerging in the area of health care.

In the health care enterprise there are actually many autonomous and independent units which are nevertheless interdependent. And nothing is constant in health care. Everything is changing all the time, even while it is being studied. All this seems to resemble something like a biologic system with its relatively independent yet interdependent cells and organ systems that must and do interact with ever changing internal and external environments. If this is true it is little wonder that the American health care system is poorly understood, since it does not fit easily into the established social, economic and political stereotypes which are better adapted to dealing with simpler and more stable systems. Could this forest, with its thickets and trees, actually be a quasi-living system with many of the characteristics of more familiar biologic systems?

If there is any reality to this analogy, the path for physicians and the medical profession in this forest begins to become clearer. In patient care physicians have developed effective methods of diagnosing and treating the ailments of a living, changing human organism. The principles of chief complaint, present illness, past history, social history, system review, physical examination, collection of objective data by laboratory and other methods, consultation with specialists in different fields when needed, a working diagnosis, plan of treatment, informed consent, agreement on what is to be done and by whom, institution of treatment program, monitoring for progress and change then making corrections to refine the diagnosis and treatment during changes in the course of the illness until the problem is solved or a steady state is reached, are principles taught to every medical student.

If the health care system indeed to some extent resembles a quasi-living organism, perhaps it is time for the medical profession to seek ways to work within the health care system that will enable it to apply some of the principles learned in medical school to the diagnosis and treatment of the ailments of this quasi-living system. At the very least some clearings might begin to be made in this forest of thickets and trees.

—MSMW

Reflections on Stones

A PRACTICAL REVIEW of how to treat renal stones, such as the Specialty Conference elsewhere in this issue, properly emphasizes that disordered urine chemistry causes unwanted crystal formation. There seem to be four mechanisms for stone formation and they are unequally important, at least at the moment. Overexcretion is the clearest one, illustrated by idiopathic hypercalciuria, primary hyperparathyroidism, hyperoxaluria and cystinuria. In each of these conditions, excessive amounts of insoluble materials are present in the urine and raise supersaturation unless a higher urine volume offsets the increased excretion rate.

Alternatively, abnormalities of urine chemistry can create conditions such that even normal excretion rates will result in supersaturation, and this is a more subtle problem. For example, low urine pH causes urine to become excessively supersaturated with respect to undissociated uric acid in patients who have gout or familial uric acid nephrolithiasis, even in the absence of hyperuricosuria.[1] On the other hand, an elevated urine pH near that of blood, as may occur in distal renal tubular acidosis, promotes the crystallization of calcium phosphate minerals even when hypercalciuria is of modest degree or absent altogether.[2] Bacteria that possess urease raise urine pH to near 9, and under this condition magnesium ammonium phosphate (struvite) can form spontaneously, especially because the organisms raise urinary ammonium content as well as pH.

A third mechanism is that of crystal-crystal interaction. At the moment, the only example of this—and not altogether proved—is in hyperuricosuric calcium oxalate stone disease. In this condition, a high intake of meat, fish and poultry lowers urine pH modestly and causes hyperuricosuria; the combination raises urine supersaturation with respect to undissociated uric

acid and promotes the formation of that crystal. Uric acid and calcium oxalate crystals share regions of identical charge spacing on selected faces,[3] so that the crystals grow on one another in an organized way, a phenomenon called epitaxy. Because of the close resemblance of their crystal surfaces, a crystal of uric acid can serve as a de novo seed crystal on which calcium and oxalate ions from solution could form an organized crystal mass and could also be a template for whose surface microcrystallites of calcium oxalate would have a high affinity. Because of template function, small calcium oxalate microcrystallites that would otherwise be harmlessly discharged into the urine might align themselves on the surface of a uric acid mass, plugging a terminal collecting duct, and in so doing form a surface of calcium oxalate monohydrate that could ultimately become a calyceal stone.

Finally, there are inhibitors of calcium oxalate crystal growth in human urine; at least some are acid glycoproteins[4,5] that may come from the renal cells themselves.[6] In theory, stones may form in some persons because of defective or reduced urine inhibitors. The measurements that would reliably allow the detection of such patients are still not available, so this subgroup remains a conjectural one.

One implication of these multiple mechanisms is that one must always evaluate patients in terms of the factors in their urine favoring the promotion of a particular crystal, and that means evaluation must begin with analysis of the stone. Calcium stones may be composed of calcium oxalate, calcium phosphate, or both, and the two crystals have somewhat different mechanisms for their production. Calcium phosphate stones form only in urine that has an average pH above 6, whereas calcium oxalate stones are insensitive to urine pH above the physiologic range of 4.5 to 7.5. Measurements of urinary oxalate excretion are essentially irrelevant in the patients whose stones are exclusively composed of calcium phosphate and crucial for patients in whom calcium oxalate stones form. Uric acid, cystine and struvite stones each pose special problems of pathogenesis in that they result mainly and respectively from acid urine, a disorder of amino acid transport and urinary infection with bacteria that have the enzyme urease. Particular metabolic disorders—for example, idiopathic hypercalciuria—may be of only minimal interest if all stones are composed of cystine or struvite.

Another implication is that one must be wary of explanations for stones, because we are still early in our understanding of the pathogenesis. Idiopathic hypercalciuria, for example, is very common and affects 5 percent of normal people; yet though it raises the risk of stones 20-fold,[7] 90 percent of people who have hypercalciuria escape stone disease. Possibly this is a matter of chance; on the other hand, the ones in whom stones form may have disorders other than supersaturation and, if these were understood, it might in the long run be easier and better to treat these factors than the urine calcium itself. So one should not rest contented with what we now know nor be excessively confident that we understand what causes stones in all cases.

A third implication is that even subtle quantitative disorders of urine chemistry may well raise risk of stone formation considerably, and they should not be dismissed without careful consideration. Urine calcium excretion seems to be a graded risk factor for calcium stones[8] and measurable excess risk of stone formation seems to appear at calcium excretion rates of 2.6 mg per kg of body weight per 24 hours, a level just above the mean of normal. The definition of hypercalciuria may have to be adjusted in relation to its effect on risk of stone, rather than being based on an arbitrary upper limit drawn from an analysis of the distribution of values in a population of normal or stone-forming people. In the same way, during the past few decades the clinical definition of high blood pressure has been adjusted because we have come to realize that risk of heart attack and stroke is increased by only a modest increment of blood pressure.

Despite the complexity of pathogenesis and the amount that still remains to be learned, diagnosis and treatment of patients with stones is now a very practical and worthwhile occupation, and should be undertaken by general physicians, urologists and internists as they encounter the disease. Based on long experience with the illness, I would offer several pragmatic points that can never be overemphasized. One should always attempt to treat patients who have recurrent disease. One should be wary of stone disease in women,[9] even those in whom only one stone has formed, as women seem to have a higher rate of admission to hospital, cystoscopy, infection and surgical treatment than men. It is crucial to know the stone count in both kidneys before beginning treatment. All of our assessment of whether our treatment is effective or not depends on knowing how many stones are available for subsequent passage, even in the absence of new stone formation. Finally, one must prepare to treat chronically, for the disease is very long-term, so the initial evaluation must be sound enough that one is willing to base a decade or more of treatment on it.

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CME *Can* Improve Patient Care

CONTINUING MEDICAL EDUCATION (CME)—the profession's mainstay of self-regulation of the quality of care—is at an awkward crossroads. One signpost indicates that present policies and practices, if continued, will be increasingly discredited as necessary but not nearly sufficient to assure that patients receive proper care from their physicians. The other signpost states that any other mandated alternative will almost surely be even less effective. These are the unsettling conclusions that emerge from the extensive and untidy literature on CME of the past 15 years. Unquestionably, both formal and informal CME increase physicians' knowledge of advances in medicine.[1-4] Equally unquestionably, there is often a substantial gap between what physicians know and what they do in the care of patients.[5-10] This dilemma is addressed directly in the study by Gullion, Adamson and Watts, appearing elsewhere in this issue. The authors show that CME can improve patient care when certain principles are followed. Further, their study is directed to office practice, an arena generally considered to be beyond the reach of evaluation, much less change. All this is a refreshing contrast to the negative reports on the widely used but usually ineffective bi-cycle model, in which CME in hospitals is based on the results of medical audits.[5,11-13] For these reasons, it is worth examining the principles underlying the reported success of Gullion and co-workers.

First, the study was carried out under the auspices of the Professional Competence Assurance Program (PROCAP), directed by Dr Malcolm S. M. Watts, a highly regarded statesman in medicine. PROCAP provided respected leadership to the effort, a prime requirement in motivating physicians to improve performance.[7,14-16] Second, PROCAP offered CME which incorporated specific techniques known to be important in bringing about change in habitual performance.[10] Foremost among these is providing feedback on each participant's own performance.[17-21] This is made more valuable by enabling each participant to compare his or her own performance with the average of all others in the study. Also, basing the report of individual performance on a total of 25 charts (and providing objective evidence that the information was abstracted reliably and accurately from these records) assures that the stated level of performance reflects habitual practice, not an occasional aberration. The fact that hypertension is one of the commonest conditions seen in the office practice of internal medicine and family practice removes CME on this subject from the realm of the esoteric and places it squarely in the category of an important, daily challenge.

Another significant feature of the method used to assess educational need was the clear distinction between the quality of record-keeping (completeness for the sake of completeness) and the quality of patient care. By selecting elements of performance that could be directly related to impact on management and its outcomes, the authors avoided the "so what" syndrome, in which CME aimed at improving documentation simply has no effect.[22] Instead, the study relied on valid criteria representing current best practice in the evaluation and management of patients with hypertension. When participants discussed these criteria with the PROCAP consultant at the outset of the study and concurred in their use, they were endorsing the criteria as valid and important indicators of the extent to which patients were receiving care that conforms to contemporary standards. Of particular significance is the observation that the criteria were readily retrieved from the charts of the great majority of physicians, again in happy contrast to the situation when "optimal" or "ideal care" criteria are used and only 40 percent to 60 percent can be located in office records.[23]

The third set of principles applied by PROCAP pertains to sound educational approaches. The CME was offered by locally recognized and accepted authorities on the management of patients with hypertension. CME given by such "influential opinion-leaders" is known to cause change in habitual practice more often than when information transfer alone is brought about by whatever means.[3,4,24,25] Also, each tutorial group was carefully selected so as to be relatively homogeneous in its level of need for CME. In this way, the consultants' discussion held the attention of the entire group. Not least, the CME was based on specific deficiencies of care common to most participants in the group, and the consultant planned the presentation accordingly. The study did not examine the relative effectiveness of the telephone conferences and the face-to-face meetings; both appeared to meet the objective of causing change in performance. One final factor influencing this change was the knowledge that the care of patients would be reexamined later, using the same essential criteria as were applied initially.

As is pointed out in the paper, the PROCAP study is descriptive and cannot be said to prove definitively that the CME as planned and presented was directly responsible for the observed improvements in performance. Controlled studies would be needed to provide the conclusive statistical and analytical evidence on this point. However, properly designed studies of this kind will be difficult to carry out and quite costly. Consequently, it may be some time before this issue is resolved to the satisfaction of those who require scientific proof. Until this becomes available, it is reasonable to look upon the PROCAP study as an important demonstration of the feasibility and the value of the approach *when the purpose of CME is to improve practice* and not merely to inform physicians of new developments.

The methods used in PROCAP will require revision

and extension if they are to be useful to physicians who wish to learn whether their overall practice, not merely in one or two conditions, meets current standards. Some means of profiling individual practices will be needed along with techniques for adequately sampling the practice content. In its present form, PROCAP points the way in which the effectiveness of ongoing CME can be readily evaluated. It is difficult to imagine a subject that has received more attention in formal CME offerings and in the professional literature than has hypertension since the advent of a full array of antihypertensive agents and greater understanding of risk factors. Yet in the PROCAP study, the majority of participants showed that they were not giving their patients the full benefit of treatment. Clearly, "more of the same" CME would not have helped, but PROCAP did.

PROCAP deserves replication in other geographic areas. The favorable response of participants suggests that the methods would be acceptable in other communities where there is sufficient leadership to mount such an effort. The costs of PROCAP were not high, considering the tangible benefits conferred upon patients. Another attractive feature is PROCAP's formula for a working partnership between academic resources and the needs of the practitioner community.

The most important reason for paying serious attention to PROCAP, beyond its simplicity of concept and effectiveness, is its practical demonstration of how medicine's traditional method of maintaining high standards of practice can be readily adapted to a valid means of rendering a public accounting for the quality of medical care. This is the high road to the preservation of self-regulation through CME.

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Case Reports

Hypothyroidism Induced by Continuous Ambulatory Peritoneal Dialysis

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THE CLINICAL MANIFESTATIONS of chronic renal failure and the high prevalence of goiter in uremic patients often suggest hypothyroidism.[1] This clinical presentation is further confused by the frequent occurrence of a low serum total thyroxine level[2,3] and free thyroxine index in cases of uremia.[2-4] Despite these biochemical alterations serum thyroid-stimulating hormone (thyrotropin) values are generally normal[3] or modestly raised.[5] It has been shown, however, that uremic persons have an increased prevalence of subnormal thyrotropin secretion in response to thyrotropin-releasing hormone testing.[6-8] This finding in conjunction with the low serum thyroxine level could be consistent with a mild secondary hypothyroidism and raises the possibility that patients with chronic renal failure may be unable to respond with an appropriate tropic hormone release to primary thyroid insufficiency. However, as the nonhormonal assessment of the metabolic state is normal in uremic patients, these patients are generally considered to be euthyroid.[5]

Although there are a number of recent studies that address the differential diagnostic problem of thyroid state in chronic renal failure,[9,10] we are unaware of an actual description of primary thyroid failure in chronically uremic patients. This report concerns two patients in whom hypothyroidism developed with elevated serum thyrotropin values while they were being treated by continuous ambulatory peritoneal dialysis. Thyroid failure was probably induced by iodine derived from povidone-iodine that had been added to the dialysate. Following discontinuance of the iodine exposure one patient reverted to a euthyroid state whereas the other remained hypothyroid.

Refer to: Gavin LA, Eitan NF, Cavalicri RR, et al: Hypothyroidism induced by continuous ambulatory peritoneal dialysis. West J Med 1983 Apr; 138:562-565.

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Methods and Patients

Continuous ambulatory peritoneal dialysis was done as previously described.[11] Following an initial period of hospital education, each patient was responsible for his or her own dialysis. The unique feature of the method was that patients were instructed to use generous amounts of povidone-iodine (Betadine) to clean catheter tips and lines and also to load new catheter tips with providone-iodine to facilitate their intraperitoneal installation. This procedure has been shown to reduce the prevalence of peritonitis, a major complication of continuous ambulatory peritoneal dialysis.[11]

Total serum thyroxine level and the free thyroxine index were measured by a two-stage competitive protein-binding method involving Sephadex binding of thyroxine I 125 on small disposable columns (Thyrolute Kit, AMES Co, Elkhart, Ind).[12] The first stage measured the total thyroxine concentration. The test serum (or standard) containing thyroxine I 125 as tracer was applied to the column at pH 11. At this pH, virtually all of the thyroxine in serum is released from its binding proteins and is adsorbed to the Sephadex. The proteins were washed through the column, which was then adjusted to a lower pH, 8.6. A solution containing thyroxine-binding globulin was passed through the column and a fraction of the adsorbed thyroxine (including tracer) was bound by the thyroxine-binding globulin. The amount of labeled thyroxine retained by the column was proportional to the amount of thyroxine originally applied in the test serum. (Columns were counted in a well counter.) In the second stage, a small aliquot (20 μl) of the test serum was applied to the same column used for the total thyroxine determination. Following a wash with pH 8.6 buffer, the column was counted again. The amount of labeled thyroxine retained after the final step was proportional to the free thyroxine concentration. The free thyroxine index result was expressed as a ratio of the final column counts for the test serum over the final column counts, for a normal reference serum (pool of normal sera). This method uses labeled thyroxine rather than triiodothyronine (T_3). Therefore it is more closely related to the free thyroxine concentration than the conventional free thyroxine index that is calculated from a T_3-resin uptake value.

The total thyroxine level was measured in the peritoneal dialysate by the previously described method for serum thyroxine.[12] Before analysis, the dialysate was concentrated tenfold in Minicon B15 concentrators (supplied by Amicon Corporation, Lexington, Mass). Total serum T_3, reverse T_3 and thyrotropin levels were measured by radioimmunoassay.[13] The serum total iodine concentration was measured by the Upjohn Company (Laboratory Procedures, Inc, Wood-

land Hills, Calif). Six uremic persons who remained euthyroid on continuous ambulatory peritoneal dialysis and 20 healthy adults with a similar age distribution to the patients were used as controls. Data presented as mean ± SD were analyzed by Student's *t* test.

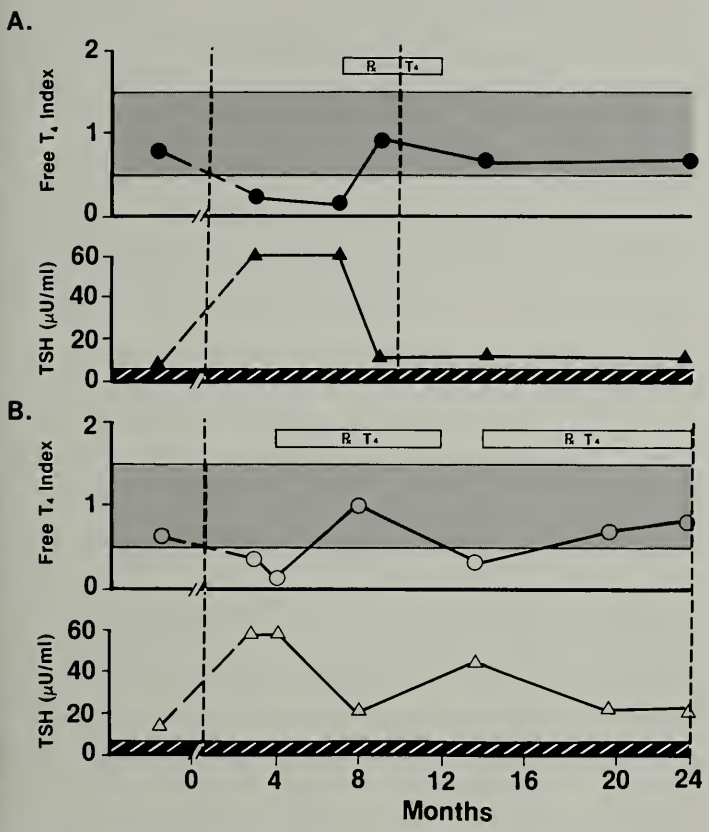

Figure 1.—Serial analyses of concentrations of serum free thyroxine (T_4) index and thyroid-stimulating hormone (thyrotropin) in two uremic patients **A** (upper panel) and **B** (lower panel) treated by continuous ambulatory peritoneal dialysis. The vertical broken lines enclose the periods of dialysis. The horizontal shaded and hatched boxes represent the normal range for the serum free thyroxine index and TSH levels, respectively. The open boxes labeled "Rx T_4" indicate the periods of thyroxine replacement. Each patient was treated by hemodialysis before the initiation of continuous ambulatory peritoneal dialysis (broken abscissa). Patient A was returned to hemodialysis following ten months of continuous ambulatory peritoneal dialysis. TSH = thyroid-stimulating hormone.

Reports of Cases

CASE 1. Serial serum free thyroxine index values and thyrotropin concentrations for the two patients who became hypothyroid during continuous ambulatory peritoneal dialysis are shown in Figure 1. Patient A (upper panel), a 55-year-old man who has hereditary nephritis, was managed on hemodialysis for six years before the initiation of continuous ambulatory peritoneal dialysis. He had a normal serum free thyroxine index value (0.65) and a thyrotropin concentration of 7 μU per ml before continuous ambulatory peritoneal dialysis. Within three months following the initiation of the ambulatory dialysis, he complained of cold intolerance, dry skin and increasing fatigue. On physical examination he had dry scaly skin, periorbital edema and absent ankle reflexes. He did not have a goiter. Results of thyroid function tests confirmed primary hypothyroidism (Table 1). The patient was still hypothyroid after seven months of continuous ambulatory peritoneal dialysis and had the low serum free thyroxine index value and elevated serum thyrotropin concentration shown in Figure 1(A). Thyroxine therapy (150 μg a day by mouth) was instituted. Within two months the free thyroxine index had returned to a normal value but the thyrotropin concentration remained modestly elevated at 9.1 μU per ml (Figure 1[A]). Serum total thyroxine level was 5.7 μg per dl, serum T_3 50 ng per dl and reverse T_3 20 ng per dl. The patient reported a pronounced amelioration of symptoms. Continuous ambulatory peritoneal dialysis had to be terminated after ten months due to an episode of peritonitis that was treated successfully. The patient was switched to hemodialysis. On review it was noted that the patient's serum iodine concentration was 320 μg per dl during continuous ambulatory peritoneal dialysis. Iodide-induced hypothyroidism was considered and the thyroxine replacement was discontinued. Figure 1(A) shows continued normal serum free thyroxine index values on hemodialysis with slightly raised serum thyrotropin values.

CASE 2. Patient B (Figure 1, lower panel) is a 75-year-old man who was being treated with hemodialysis for a year before switching to continuous ambulatory peritoneal dialysis. His uremia had been attributed to

TABLE 1.—*Serum Thyroid Function Tests in Uremic Patients on Continuous Ambulatory Peritoneal Dialysis (CAPD)*

Group	*Number*	*Total Thyroxine (μg/dl)*	*Free Thyroxine Index**	*Total T_3* (ng/dl)*	*Total Reverse T_3* (ng/dl)*	*Thyrotropin* (μU/ml)*
Uremic Patients Who Are Hypothyroid						
Patient A after 3 months CAPD		3.1	0.22	44	7	>60
Patient B after 4 months CAPD		4.5	0.15	50	5	>60
Uremic Patients Who Are Euthyroid						
Before CAPD†	6	6.4± 1.3	0.7±0.2	59± 10§	23± 5	3.9±1.0
CAPD for 2 months	6	6.5± 1.7	0.8±0.4	67± 12§	19± 6	5.0±1.1
CAPD for 8 months	6	6.3± 1.9	0.7±0.3	60± 15§	21± 7	4.1±0.9
Range of Controls	20	4.6−10.2	0.4−1.2	82−122	<5−34	1.7−6.5

T_3 = triiodothyronine.

*Data are presented as mean ± SD.
†Four patients had hemodialysis for 3 to 30 months.
§$P < .001$ uremic persons versus normal subjects.

an obstructive uropathy consequent to grade IV prostatic carcinoma. Medication included diethylstilbestrol (1 mg daily by mouth). He was clinically euthyroid before continuous ambulatory peritoneal dialysis, despite a thyrotropin level of 14.5 μU per ml (Figure 1-[B]). Within three to four months following the initiation of continuous ambulatory peritoneal dialysis he complained of tiredness, cold intolerance and hoarseness. On physical examination he had bradycardia and moderate ankle edema but no goiter, facial puffiness or sluggish reflexes. Results of thyroid function tests indicated primary thyroid failure (Table 1). Serum iodine concentration was 275 μg per dl. The use of povidone-iodine in the continuous ambulatory peritoneal dialysis protocol was discontinued. Thyroxine replacement (150 μg a day) was initiated and maintained for eight months, with a good clinical response. Within four months after beginning thyroxine therapy the serum free thyroxine index was 0.99 and the thyrotropin level 24 μU per ml (Figure 1[B]). The associated serum total thyroxine level was 10.9 μg per dl. Following a further four months, the thyroxine replacement therapy was stopped; however, the patient became clinically and biochemically hypothyroid within ten weeks (Figure 1[B]). Thyroxine replacement was reintroduced (250 μg a day) with correction of the clinical features and the low serum free thyroxine index (Figure 1[B]). Despite the thyroxine therapy the serum thyrotropin concentration remained elevated at 23 μU per ml (at 19 months) and 21 μU per ml (at 24 months).

Table 1 also shows the thyroid hormone profiles in the six control subjects receiving prolonged continuous ambulatory peritoneal dialysis who remained euthyroid. Mean serum total thyroxine level, free thyroxine index, thyrotropin and reverse T_3 values in these uremic persons were similar to those of the control group both before continuous ambulatory peritoneal dialysis and at the time points studied during the dialysis. Their mean serum total T_3 concentration was significantly less ($P<.001$) than the control mean irrespective of therapy.

Tests for antithyroid antibodies (microsomal and thyroglobulin) were negative in both hypothyroid patients. The serum total iodide level was elevated in patient A (320 μg per dl) and patient B (275 μg per dl) during the initial hypothyroid phase while receiving continuous ambulatory peritoneal dialysis. Discontinuation of continuous ambulatory peritoneal dialysis in patient A and the povidone-iodine use in patient B caused a return to near normal of the serum iodine concentration at 13.8 μg per dl and 20 μg per dl, respectively (normal serum total iodine level, 4 to 9 μg per dl). The mean serum iodine level in three of the patients receiving continuous ambulatory peritoneal dialysis but who were euthyroid was 10 ± 2.7 μg per dl. The mean dialysate total thyroxine concentration in specimens from five euthyroid persons receiving continuous ambulatory peritoneal dialysis was 3.6 ± 0.7 μg per liter (unconcentrated). Each patient was dialyzed against 8 liters of solution per day. Thus the mean daily loss of thyroxine by this route was about 29 μg.

Discussion

This report shows that uremic patients can respond to thyroid failure with an appropriate thyrotropin elevation. In previous reports it had been suggested that the hypothalamic pituitary thyroid axis was depressed in uremic patients, whether or not they were on hemodialysis, to explain the inappropriately low thyrotropin levels noted in uremic persons with low serum thyroxine and triiodothyronine values.[2,6,7] Thus it was postulated that the basal serum thyrotropin level was unreliable and might not reflect a true primary hypothyroid state.[14,15] This report shows that thyrotropes in uremic patients can respond appropriately to thyroid failure.

Iodine seems to have been the major factor responsible for the development of the hypothyroidism following the initiation of continuous ambulatory peritoneal dialysis in both of our patients. The lavish use of povidone-iodine in the dialysis protocol resulted in very high levels of serum iodine consequent to peritoneal absorption. Hypothyroidism resulting from chronic intraperitoneal iodine has never before been reported. In normal persons the iodine block in thyroid hormone synthesis (the Wolff-Chaikoff effect) is usually transient and of little clinical consequence,[16,17] unless there is underlying preexisting thyroid pathology.[18] Neither of our patients had a history of thyroid disease, a goiter or tests positive for serum antithyroid antibody. However, patient B did have an elevated serum thyrotropin level (14 μU per ml) before continuous ambulatory peritoneal dialysis, suggesting that he may have had latent hypothyroidism and a limited thyroid reserve.[19] Moreover, there may be impaired intrathyroidal metabolism in uremic persons that could predispose them to a persistent iodide block.[2,7] In addition, patient A's condition reverted to normal once he was removed from the iodide exposure and the high serum iodide level was corrected. Finally, three of the patients who remained euthyroid while receiving continuous ambulatory peritoneal dialysis had only modest iodine exposure, which indicates that pharmacologic doses intraperitoneally are needed to induce a thyroid block.

This is the first observation that significant amounts of thyroxine are lost in the peritoneal dialysate. This loss probably reflects both free and protein-bound thyroxine. Continuous ambulatory peritoneal dialysis is characterized by a significant daily loss of albumin in the dialysate.[20] Because thyroxine-binding globulin has a similar molecular weight to that of albumin, substantial amounts of this protein (the major carrier of serum thyroxine) are probably also lost in the dialysate. We previously showed a significant positive correlation between the degree of proteinuria (albuminuria) and urinary thyroxine-binding globulin loss in nephrotic patients.[21] Thus, future studies on persons receiving continuous ambulatory peritoneal dialysis should show the presence of significant amounts of thyroxine-bind-

ing globulin and other thyroid hormones in the dialysate.

The rate of dialysate thyroxine loss (29 μg a day) by these patients was equivalent to about 30 percent of the normal human thyroxine production rate.[22] Despite this thyroxine loss, most of our patients on continuous ambulatory peritoneal dialysis were able to compensate and maintain a euthyroid state. Our studies did not show a transient increase in serum thyrotropin level, which would have reflected this compensatory process. Detailed analyses of the serum thyroid hormones were not done during the initial phase of the peritoneal dialysis (<1 month). More detailed studies during the initiation of this treatment on a greater number of patients should detect the compensatory process. A recent report[20] supports our finding that most patients receiving continuous ambulatory peritoneal dialysis remain euthyroid. The long-term follow-up (>12 months) was confined to only a few cases, however, so conclusions regarding the possible development of hypothyroidism cannot be reached. Because the incidence of subclinical or latent hypothyroidism in the general population is high (3.0 percent)[23] and may be even greater in the uremic population,[4] patients receiving continuous ambulatory peritoneal dialysis may be especially susceptible to thyroid failure. Patient B may have had latent hypothyroidism (thyrotropin level 14 μU per ml) before dialysis and may not have been able to compensate for the extra loss of thyroxine via the dialysate even after his serum total iodine level had returned to normal. As a consequence he remained hypothyroid while receiving continuous ambulatory peritoneal dialysis. Once this type of dialysis gains wider acceptance in the long-term management of chronic renal failure, an increased prevalence of clinical hypothyroidism might be anticipated in this population even when excessive exposure to iodine is avoided.

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Corticosteroid Therapy and Death in Cases of Adult Bronchial Asthma

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THE EFFICACY of corticosteroids in the treatment of acute bronchial asthma is well documented and has led to recommendations that corticosteroids be used early in treating status asthmaticus.[1-4] An opposing view is that corticosteroids be given only after other therapies have failed; this is based on concern for the potential complications of steroid use.[5-6] Whereas the efficacy and side effects of corticosteroids in the treatment of bronchial asthma are well recognized, their role in fatal cases is less well defined. We report deaths in five cases of bronchial asthma and analyze the role of corticosteroids in these fatal cases. The treatment of severe asthma is often by nonspecialty physicians. An increased awareness of the complexities of corticosteroid use in bronchial asthma may prevent fatalities.

From 1973 to 1980 there were 530 patients with a history of bronchial asthma admitted to Wadsworth Veterans Administration (VA) Hospital (Los Angeles). Of these patients 192 were admitted primarily for an exacerbation of bronchial asthma, 41 having multiple admissions, for a total of 280 admissions during this period. Five fatal cases were identified among these patients treated for asthma. In one patient corticosteroid

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ABBREVIATIONS USED IN TEXT

$Paco_2$ = partial arterial carbon dioxide pressure
Pao_2 = partial arterial oxygen pressure
VA = Veterans Administration

therapy was withheld because of a diagnosis of acute pancreatitis thought to be due to a single 60-mg dose of intravenously given methylprednisolone. Failure to institute corticosteroid therapy was probably a factor in the deaths of two others. The development of unusual infections complicating corticosteroid therapy contributed to the death of the remaining two patients.

The objective of this review is to emphasize the value of early use of corticosteroids in status asthmaticus and the need for surveillance for complications of treatment.

Reports of Cases

CASE 1. A 55-year-old man was admitted for shortness of breath that had lasted for two days. The patient had a six-year history of bronchial asthma and had been treated with oral and inhaled bronchodilators. During the two months before admission, the patient was seen in a community hospital emergency department five times for shortness of breath. He had symptomatic improvement with intermittent positive-pressure breathing treatments with isoetharine and on each occasion was discharged on a regimen of theophylline with ethylenediamine (aminophylline) alone.

The day before admission the patient was seen at another hospital where he was noted to have respirations of 34 a minute, a heart rate of 112 beats a minute and diffuse expiratory wheezing. Arterial blood gas determinations made while the patient was breathing room air showed a pH of 7.45, a partial arterial carbon dioxide pressure ($Paco_2$) of 36 mm of mercury (normal 35 to 40) and a partial arterial oxygen pressure (Pao_2) of 57 (normal 76 to 84, corrected for age). Hematocrit was 43 percent. He was given aminophylline intravenously and intermittent positive-pressure breathing treatment with isoetharine and was sent home following subjective improvement.

The next day the patient returned to the same emergency department with a reexacerbation. Intravenous administration of aminophylline was restarted and after intermittent positive-pressure breathing treatment with isoetharine was given, the patient was transferred to Wadsworth VA Hospital. Initial assessment showed a thin man appearing to be in moderate respiratory distress. His temperature was 37.0°C (98.6°F), pulse rate 112 a minute, respirations 27 per minute and blood pressure 110/63 mm of mercury. Chest examination showed diffuse expiratory wheezing. Peak expiratory flow rate was 120 liters per minute. An arterial blood gas study was not done. The patient was treated with intravenous aminophylline, aerosolized isoetharine delivered by hand-held nebulizer and supplemental oxygen given at 2 liters a minute. Peak expiratory flow rates did not improve during three hours of treatment in the emergency department. He received 0.25 mg of terbutaline sulfate subcutaneously and was transported to the ward with oxygen being given nasally.

While the patient was in transit from the emergency department to the ward a coughing spell developed, followed by severe shortness of breath. He had respiratory arrest and resuscitative measures were instituted. Arterial blood gas determinations while the patient was receiving nasal oxygen showed a pH of 7.0, a $Paco_2$ of 102 mm of mercury and a Pao_2 of 28. An electrocardiogram showed sinus tachycardia. There was no pneumothorax noted on a chest roentgenogram. Hematocrit was 47 percent. Difficulty in maintaining adequate ventilation was encountered and the patient died. Postmortem findings showed diffuse mucous plugging of the bronchioles.

Comment. With a history of five visits to an emergency department for asthmatic exacerbations in the two months before admission, the patient should have been promptly admitted. The lack of improvement in peak expiratory flow after treatment with aminophylline and sympathomimetics in the emergency department should have prompted the use of more aggressive therapy, including administration of corticosteroids and admission to an intensive care unit rather than a ward. The hemoconcentration reflected by the rise in hematocrit in a 24-hour period suggested that fluid therapy was not optimal for replacing fluid deficit.

CASE 2. A 59-year-old man was admitted for treatment of paralysis agitans (Parkinson's disease). He had a 20-year history of asthma treated with inhaled sympathomimetics. On the fifth hospital day he was noted to be short of breath. Room air arterial blood gas determinations showed a pH of 7.40, a $Paco_2$ of 34 mm of mercury and a Pao_2 of 70 mm of mercury. He was started on a regimen of aminophylline, 200 mg by mouth every six hours. In the evening of the same day acute respiratory distress developed. His mental state was depressed and examination of the chest showed diffuse inspiratory and expiratory wheezing. Arterial blood gas determinations made while the patient was breathing room air showed a pH of 7.21, a $Paco_2$ of 74 mm of mercury and a Pao_2 of 40 mm of mercury. Intravenous administration of aminophylline was started. He was also given 0.3 mg of terbutaline subcutaneously, intermittent positive-pressure breathing treatment with isoetharine and nasal oxygen at 2 liters a minute. Two hours later arterial blood gas studies done with the patient receiving 2 liters a minute of supplemental oxygen showed a pH of 7.37, a $Paco_2$ of 29 mm of mercury, and a Pao_2 of 80 mm of mercury. The patient's condition improved and he was kept on the ward overnight. Corticosteroid therapy was not instituted.

He was transferred to the medical intensive care unit the next morning because of recurrence of depressed mental state and respiratory distress. Endotracheal intubation and mechanical ventilation were required.

Bilateral tension pneumothoraces developed and the patient had cardiorespiratory arrest. Bilateral chest tubes were inserted during resuscitation. The patient became comatose and died several days later. No postmortem examination was done.

Comment. The severity of this patient's asthmatic exacerbation should have prompted the use of more aggressive therapy, including the administration of corticosteroids and earlier transfer to an intensive care unit. This could have averted his subsequent deterioration and obviated the need for continued use of intermittent positive-pressure breathing treatment or mechanical ventilation.

It is possible that bilateral pneumothoraces associated with intermittent positive-pressure breathing treatment accounted for his deterioration[7] and mechanical ventilation then aggravated the condition.

CASE 3. A 51-year-old man was admitted for treatment of shortness of breath. He had a seven-year history of severe asthma requiring admission to hospital and corticosteroid treatment on two previous occasions. The day before admission he was seen in the emergency department for shortness of breath. Arterial blood gas determinations made while he was breathing room air showed a pH of 7.40, a $Paco_2$ of 42 mm of mercury and a Pao_2 of 63 mm of mercury. He was given aminophylline intravenously and 60 mg of methylprednisolone. He improved subjectively and was sent home.

The following day the patient returned to the emergency department because he had epigastric pain. He was admitted with a diagnosis of pancreatitis. Serial serum amylase levels during the next two days were 176, 635 and 400 mg per dl (normal <190). A two-hour urinary diastase level was 3,069 mg per dl (normal <600). He was thought to have acute pancreatitis, possibly due to the corticosteroid that he received intravenously the day before admission. He continued to receive aminophylline and inhaled sympathomimetics. Corticosteroid therapy was withheld.

His abdominal pain subsided six days after admission. The patient's oral bronchodilator therapy was interrupted in preparation for an upper gastrointestinal radiographic study, the findings of which were unremarkable. He was subsequently discharged, though he noted increasing shortness of breath.

On the morning after discharge the patient was examined in the allergy clinic and was observed to have pronounced wheezing and shortness of breath. He was admitted to the chest service and given fluids and aminophylline intravenously and inhaled isoproterenol. The patient seemed to respond clinically. Corticosteroid therapy was withheld for fear of precipitating pancreatitis again. At 3 the following morning the patient was found slumped over a chair, cyanotic and without a palpable blood pressure. Cardiorespiratory resuscitation was unsuccessful. Postmortem examination showed diffuse mucous plugging of the airways. Careful microscopic examination of the pancreas showed no evidence of pancreatitis.

Comment. The presence of extensive mucous plugging in the airways suggests that this patient died in status asthmaticus. The diagnosis of acute pancreatitis due to the intravenous administration of a single 60-mg dose of methylprednisolone resulted in the withholding of corticosteroids from this patient who had clearly shown a need for this medication on two previous occasions. In two recent critical reviews on drug-induced pancreatitis,[8,9] a probable association was noted between corticosteroid administration and acute pancreatitis. The duration of corticosteroid treatment before the onset of symptoms of pancreatitis ranged from one week to seven years and averaged 37 weeks; dosages of corticosteroid ranged from 8 mg to 200 mg of prednisone a day.[8] Fatal cases in adults have been reported.[10-12] There is, however, no report of a single dose of corticosteroid precipitating acute pancreatitis. The worsening condition that developed after oral bronchodilator therapy was interrupted in preparation for an upper gastrointestinal study confirms the need for continuous monitoring and treatment of asthmatic patients. In the event oral bronchodilator therapy is interrupted, aerosolized and intravenous medication should be continued.

CASE 4. A 50-year-old man was admitted because of shortness of breath for two days. He had a 20-year history of bronchial asthma and two previous hospital admissions for status asthmaticus.

At the time of admission his temperature was 36.8°C (98.2°F), respirations 44 per minute and blood pressure 130/80 mm of mercury. Chest examination showed diffuse expiratory wheezing. Findings on the chest film were normal. Arterial blood gas studies done while the patient was breathing room air showed a pH of 7.49, a $Paco_2$ of 30 mm of mercury and a Pao_2 of 57 mm of mercury. He responded to treatment that included intermittent positive-pressure breathing with isoetharine and intravenous administration of aminophylline. On the fifth hospital day an acute episode of shortness of breath developed. His forced vital capacity was 2.55 liters and forced expiratory volume in one second was 1.00 liter. Intravenous administration of methylprednisolone (125 mg every six hours) was started and continued for seven days. The forced vital capacity and forced expiratory volume in one second improved to 4.34 liters and 1.44 liters, respectively, and he was then treated with corticosteroids given by mouth.

On the 12th hospital day a temperature of 38.9°C (102°F) developed. A chest roentgenogram showed left lower lobe consolidation. Penicillin and amikacin sulfate were given, with no apparent response. On the 19th hospital day a generalized seizure occurred and he had a cardiorespiratory arrest. Resuscitation efforts were unsuccessful. Postmortem examination showed findings of an old, as well as a recent but nonacute, myocardial infarction and left lower lobe bronchopneumonia due to *Legionella pneumophila*.

Comment. Legionnaires' disease was not suspected in this patient. The acquisition of the disease was probably related to the immunosuppressive effects of corti-

TABLE 1.—*Relevant Factors in Asthma Deaths and Their Presence (+) or Absence (−) in Our 5 Cases*

	Cases				
	1	*2*	*3*	*4*	*5*
Long history of asthma	+	+	+	+	+
Previous admission with severe attack	−	−	+	+	+
Recent hospital admission or emergency care	+	−	+	−	−
Insufficient treatment or assessment or intensive care	+	+	+	−	−
Underuse of steroids	+	+	+	−	−
Pneumothorax	−	+	−	−	−
Unusual infections	−	−	−	+	+

costeroids. In cases of legionnaires' disease identified at Wadsworth VA Hospital, 9 of 24 patients received pharmacologic doses of corticosteroids within ten days of the onset of illness.[13] The disease was fatal in immunosuppressed hosts unless specific therapy was given.

CASE 5. A 43-year-old man was admitted for evaluation of a two-week history of fever, chills, worsening dyspnea and cough unresponsive to administration of tetracycline. He had a history of childhood asthma. He was admitted to hospital for exacerbations of asthma in 1970 and 1974, and on each occasion was treated with intravenous administration of methylprednisolone, in addition to aminophylline and inhalation of sympathomimetics. Outpatient treatment consisted of the administration of prednisone, 20 mg every other day, aminophylline and hydroxyzine hydrochloride, and inhalation of isoproterenol. There was no history of intravenous drug use or previous heart disease. Examination on admission showed his temperature to be 38.2°C (100.8°F), pulse rate 120 beats per minute, blood pressure 100/60 mm of mercury and respiratory rate 24 a minute. Examination of the chest showed an increase in the anteroposterior diameter, hyperresonance and diffuse wheezing. No cardiac murmurs or gallops were heard. Hepatomegaly was noted. Following admission, laboratory studies obtained values that included a hematocrit of 36 percent and a leukocyte count of 29,200 per cu mm, with 77 percent neutrophils, 20 percent band forms and 3 percent lymphocytes. Arterial blood gas determinations made while the patient was breathing room air showed a pH of 7.49, a $Paco_2$ of 36 mm of mercury and a Pao_2 of 65 mm of mercury.

The patient was treated with intravenous administration of aminophylline, ampicillin and methylprednisolone (125 mg every six hours). Blood cultures grew *Pseudomonas aeruginosa*. Gentamicin sulfate and carbenicillin therapy was started and the prednisone dosage tapered to 10 mg given every other day. The patient continued to be febrile and subsequent blood cultures continued to grow *P aeruginosa*. Extensive diagnostic workup, including laparotomy and right heart catheterization, did not reveal the site of infection. After eight weeks of receiving antibiotic therapy, grand mal seizures developed and he had a cardiorespiratory arrest. He became comatose and died.

Postmortem examination showed polypoid vegetations on the mitral valve with perforation of the anterior and posterior leaflets. There was no evidence of rheumatic scarring. Amyloid involvement of the blood vessels of the heart, liver, kidneys, pancreas, adrenal glands and lymph nodes was found on microscopic examination.

Comment. A detailed analysis of this case was previously reported.[14] For our present discussion it is enough to point out that this patient clearly required corticosteroids for control of acute and chronic asthma. Corticosteroids affect host defense mechanisms and could have contributed to the development of *P aeruginosa* endocarditis and the lack of response to appropriate and adequate antibiotic therapy.

Discussion

Although many factors are associated with death from asthma, underuse of corticosteroids has been incriminated as a specific cause of death.[15-18] Other factors include the following: a long history of asthma,[19] previous admissions for severe attacks,[15,16,19] recent hospital admission,[15,16] insufficient assessment and treatment,[16,17,19] cardiac arrhythmia,[20] pneumothorax,[7,21] excessive diurnal variation in peak expiratory flow rates[22] and delay in getting treatment at the hospital.[23]

Table 1 summarizes the presence of these factors in our five cases. All of our patients had a long history of asthma and three had previous admissions for severe attacks. One had been recently admitted to hospital and another had several recent emergency department visits. Insufficient assessment and treatment were evident in three cases. Underuse of corticosteroids was present in three cases. Pneumothorax developed in one patient who received intermittent positive-pressure breathing therapy and two had fatal infectious complications. The fatal outcome in cases 1, 2 and 3 could possibly have been averted with the use of corticosteroids. The last two patients succumbed to unusual infections that developed in the presence of corticosteroid use and its immunosuppressive effects. Our series of five patients thus shows that the use of corticosteroids in the management of status asthmaticus can be a demanding situation for a physician. It requires recognition of the need for corticosteroid therapy, as well as surveillance for complications of treatment.

The recognition of severe asthma during an acute attack, however, may be the most important factor in preventing death. Respirations of more than 35 per minute, a heart rate of more than 120 per minute, the presence of pulsus paradoxus, a silent chest in a symptomatic patient, the use of accessory muscles of breathing, altered consciousness and an exhausted patient are all ominous clinical signs. An elevated $Paco_2$ level, respiratory acidosis, hypoxemia and a significantly decreased forced expiratory volume at one second (less

than 800 ml) or a decreased peak flow rate (less than 60 liters per minute) are laboratory findings that indicate a severe attack. All of these factors should be assessed while a patient is receiving maximal bronchodilator therapy. If a patient fails to respond, intravenous corticosteroid therapy should be instituted promptly, with the recognition that the onset of effect on the asthmatic airway following intravenous administration of a corticosteroid has been determined to be two hours.[24,25] A delay in the use of the drug deprives a patient of its potential benefits. Corticosteroids should also be administered to patients with severe asthmatic exacerbations who have received systemic corticosteroids in the previous 12 months.

The development of infections in patients immunosuppressed by corticosteroids is well documented. Although infrequent, fatal infections can occur in asthmatic patients receiving corticosteroids. Patients must be carefully monitored for infections and other complications. Prompt treatment of complications helps avert fatal outcomes.

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Chest Wall Stimulation for Pacemaker Inhibition

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PROPER SENSING FUNCTION of a ventricular-inhibited (demand) pacemaker generator requires a stable intracardiac signal having sufficient amplitude, duration and slew (rate of change in voltage).[1-3] Intracardiac signals that do not meet the sensing requirements of the pacemaker generator may be sensed intermittently or not at all, resulting in the delivery of inappropriately early pacing stimuli. If these stimuli fall during a critical time period during ventricular repolarization, repetitive ventricular beating may result. Chest wall stimulation, during which electrical stimuli are delivered to the body surface via an external pacemaker generator, can produce signals capable of being sensed by the implanted demand pacemaker generator, which will then inhibit.[4]

We report the case of a patient with acute myocardial infarction in whom chest wall stimulation was used successfully for 12 hours in order to inhibit an implanted pulse generator that caused repeated episodes of ventricular tachycardia and fibrillation because of failing to sense intracardiac signals.

Report of a Case

A 77-year-old man was admitted to the coronary care unit complaining of chest pain unrelieved by sublingual nitroglycerin. Three years earlier he had had a nontransmural anterior myocardial infarction complicated by bradycardia-tachycardia syndrome and bundle branch block, and a permanent unipolar ventricular demand pacing system (Ela Stilith 60) was implanted and its rate set at 51 per minute. Because of stable postinfarction angina, shortness of breath and periodic supraventricular tachycardias, the patient was placed on a daily regimen of 0.25 mg of digoxin, 1.4 grams of quinidine gluconate, 80 mg of propranolol and sublingual nitroglycerin tablets.

On physical examination at admission the patient appeared to be in respiratory distress, coughing blood-tinged sputum. Blood pressure was 150/110 mm of mercury and apical pulse 100 per minute and irregular. Pertinent findings included normal central venous pressure, bilateral rales, a sustained nondisplaced left ventricular apical impulse and an S_3 gallop. Results of the following laboratory studies were within normal limits: complete blood count, analysis of urine, blood urea nitrogen level and electrolyte determinations, including serum potassium. Arterial blood gas analysis showed

Refer to: Goldschlager N, Andrews B: Chest wall stimulation for pacemaker inhibition. West J Med 1983 Apr; 138:569-573.

From the Cardiology Division and Department of Medicine, San Francisco General Hospital Medical Center, and the Department of Medicine, University of California, San Francisco, School of Medicine.

Submitted, revised, March 17, 1982.

Reprint requests to Nora Goldschlager, MD, Cardiology Division, San Francisco General Hospital Medical Center, San Francisco, CA 94110.

pH of 7.2; Pco_2 was 38 and Po_2 51 mm of mercury. An x-ray study of the chest showed cardiomegaly and pulmonary edema. An electrocardiogram showed atrial fibrillation, rapid ventricular rate, right bundle branch block pattern and acute transmural anterior wall myocardial infarction. Pacemaker sensing and pacing functions were normal.

The patient was treated with oxygen, morphine sulfate and intravenously given furosemide with some resolution of his pulmonary edema. Serial electrocardiograms and creatine kinase determinations documented acute myocardial infarction. The quinidine gluconate and propranolol administration was discontinued. The patient's course over the ensuing 24 hours was complicated by low cardiac output, congestive heart failure, intermittent atrial fibrillation with rapid ventricular rate (requiring additional doses of intravenous digoxin to a serum level of 2.9 μg per ml to lower ventricular rate) and episodes of ventricular tachycardia, flutter and fibrillation for which he received lidocaine intravenously. Many of these ventricular arrhythmias, as well as normal QRS complexes, were not sensed by the pacemaker, which continued to deliver pacing stimuli (Figures 1 through 3). On two separate occasions pacemaker-induced ventricular flutter and fibrillation resulted from unsensed spontaneous QRS complexes (Figure 4); these episodes were successfully treated with electrical defibrillation.

Because of the life-threatening nature of the pacemaker-induced ventricular arrhythmias, the implanted pulse generator was inhibited using the technique of chest wall stimulation. Suction cup electrodes were placed on the skin as follows: one at the fourth left interspace at the left sternal border, where the intracardiac (cathodal) electrode was considered to be located; and the other over the implanted pacemaker generator, which served as the anode in this unipolar pacing system. The skin electrodes were then connected to an external pacemaker generator (Medtronic Model 5880) via cables whose ends are specially designed to fit into the terminals of the external pulse generator. The rate of the external generator was set to 70 per minute in order to override the rate of the implanted generator, and the mode of function set to asynchronous (fixed rate). The external pacemaker generator was then turned on and its output gradually increased. At about 3 mA the chest wall stimuli were of sufficient amplitude to be sensed by the implanted pulse generator, which was consequently inhibited.

Chest wall stimulation was continued over the next 12 hours, without patient discomfort and without further pacer-induced arrhythmias. Despite aggressive

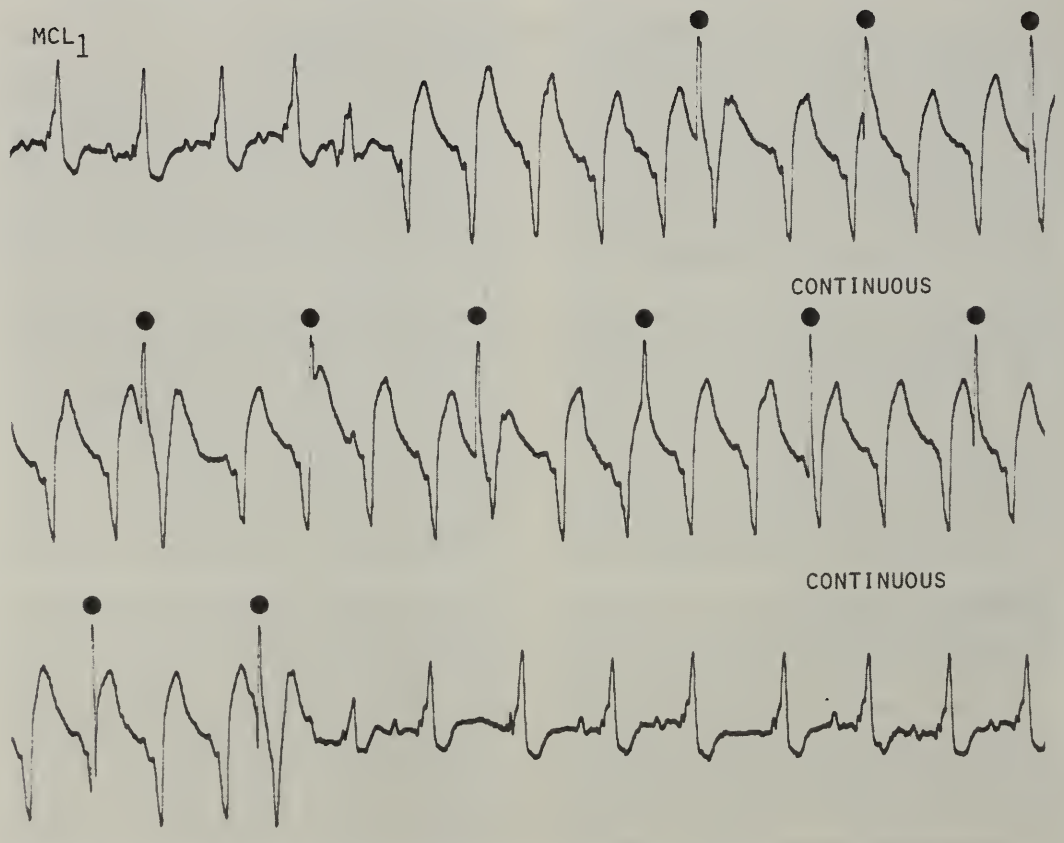

Figure 1.—These three continuous MCL_1 rhythm strips show sinus rhythm with right bundle branch block, a fusion complex (fifth QRS complex) and ventricular tachycardia. The ventricular tachycardia is initially sensed by the pacemaker generator as evidenced by the absence of pacing artifacts. Toward the end of the top strip, however, pacing artifacts occur, and continue at regular intervals corresponding to a rate of about 50 per minute **(closed circles).** Ventricular capture by the pacemaker occurs (third and eighth QRS complexes in the middle strip and fifth QRS complex in the bottom strip), and may actually have fortuitously resulted in tachycardia termination.

medical management, however, the patient died on the third hospital day.

Discussion

The occurrence of acute myocardial infarction provides a potential milieu for pacemaker-related problems due both to undersensing and to changing myocardial stimulation thresholds, as well as changing thresholds for the development and maintenance of repetitive ventricular arrhythmias, including ventricular fibrillation.

Sensing problems in this patient could have been due to electrode catheter displacement, pulse generator malfunction or undersensing resulting from intracardiac signals of too low a voltage, too slow a rate of change of voltage (slew) or prolonged duration (or both of the latter). Pulse generator malfunction was unlikely, as the lithium-powered unit had been in place for three years; in addition, normal pacing function was present, and normal sensing capability was shown by its inhibition by chest wall stimuli. Electrode catheter displacement, albeit possible, was also extremely unlikely because (1) the lead had been in place for three years, (2) *ventricular* pacing was occurring, (3) x-ray films of the chest did not suggest major changes in position and (4) both the pacing artifact axis and contour and axis

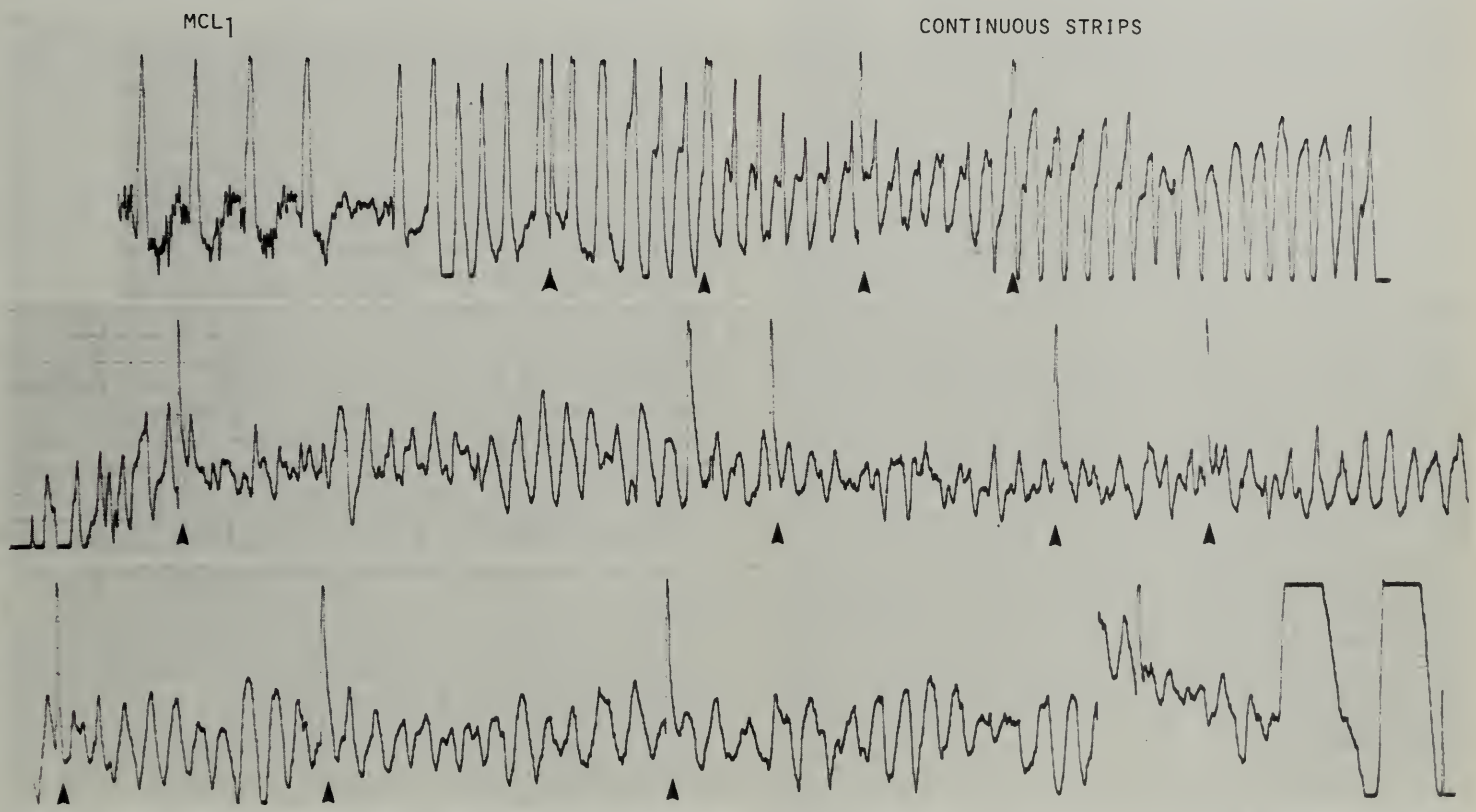

Figure 2.—These continuously recorded MCL_1 rhythm strips show atrial flutter with rapid (2:1 and 3:1) ventricular response. Polymorphous ventricular tachycardia degenerating to ventricular fibrillation occurs abruptly. The pacemaker does not sense the tachycardia and fibrillation, as indicated by the delivery of pacing artifacts **(arrows)**. However, since the interval between pacing artifacts is not regular at 1,200 ms (50 beats per minute), it may be assumed that intermittent sensing of ventricular electrical activity is occurring. In the middle strip two pacing artifacts occur at an interval of about 600 ms (100 beats per minute). As the magnetic rate of this pacemaker generator is the same as the automatic (pacing) rate, conversion to fixed rate mode in the presence of electrical "noise" caused by the ventricular tachycardia cannot explain the observation.

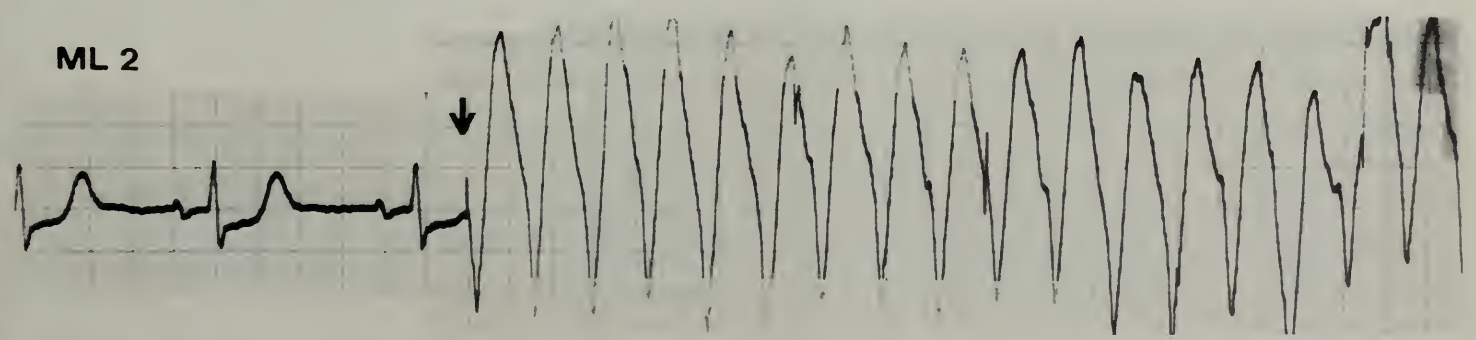

Figure 3.—Failure to sense a sinus-initiated QRS complex results in the delivery of a pacing stimulus at the onset of the inscription of the T wave, with consequent development of ventricular tachycardia. Partial sensing of this tachycardia is occurring, as evidenced by the intermittency of the pacing artifacts. Note that the unsensed QRS complex appears on the surface electrocardiogram to be no different from other, sensed, QRS complexes, illustrating that the surface electrocardiogram does not reflect the quality of intracardiac signals.

of paced QRS complexes were identical to those recorded at the time of pacing system implant.

The most likely cause of sensing problems in this patient lay in the suboptimal nature of the intracardiac signal. Signals of borderline voltage, long duration or poor intrinsic deflection may fall below the sensing threshold of a permanent pacemaker.[1,3] Such signals may occur in the setting of conduction system disease,[5] during acute myocardial infarction,[6,7] when impulses originate in ventricular tissue, when abnormalities of pH or electrolytes—especially potassium—are present, and when high concentration of type I antiarrhythmic agents (quinidine, procainamide, disopyramide) exist. As several of these conditions may coexist in very ill patients, it is not always possible to define a precise cause of pacemaker undersensing. In our patient, pacemaker undersensing was not present initially but developed in the hospital, and was probably contributed to by a deteriorating hemodynamic and electrophysiologic status.

During acute myocardial infarction, changing thresholds for myocardial stimulation and ventricular fibrillation can result in failure to capture by the pacemaker or proclivity to pacemaker-induced ventricular arrhythmias (or both). While pulse generators now in use have energy outputs too low to precipitate arrhythmias under the *usual* clinical circumstances in which they are implanted, such arrhythmias may occur during myocardial ischemia and infarction,[8-11] hyperadrenergicity[12,13] and premature systoles.[14-16] At no time did sufficient increase in myocardial stimulation threshold develop in our patient to result in failure to pace; his problems were related entirely to inability of the generator to sense spontaneous QRS complexes, resulting in delivery of premature pacing stimuli relative to the spontaneous RR cycle length, which in turn caused potentially lethal arrhythmias.

The changing quality of intracardiac signals that causes intermittent nonsensing of spontaneous QRS complexes might be related to (1) ischemia and necrosis, (2) metabolic acidosis, (3) ventricular dilatation, (4) myocardial cellular edema, (5) failure of impulse conduction in the area of the electrodes and (6) alterations in local drug or electrolyte concentrations, specifically type I antiarrhythmic agents and potassium.

While metabolic acidosis and alkalosis have been shown in dogs and in humans to result in an increase in myocardial stimulation threshold,[13-17] the import of pH changes on the intracardiac electrogram, and therefore on pacemaker sensing function, is not known. It is conceivable that metabolic acidosis, as is seen in cardiogenic shock or cardiac arrest, could cause changes in voltage or duration of intracardiac signals such that the resulting electrogram is suboptimal for sensing. Systematic study of this possibility is feasible, and warranted.

Myocardial cellular edema and ventricular dilatation have been shown to produce sufficient distortion of a depolarization signal to result in suboptimal electrograms for sensing.[6,7] Signal distortion in this setting might be due to slowing of impulse transmission and, in bipolar pacing systems, to a change in bipolar axis relative to the depolarization pathway, such that the impulse yields signals of equal magnitude at each electrode, resulting in small or zero bipolar voltage.[18] While these conditions might be expected to be associated with a concomitant increase in myocardial stimulation threshold and thus in failure to pace, their simultaneity is in fact not often observed unless the patient is moribund.

Contributing to the pacemaker-related arrhythmias in our patient could have been lower-than-normal thresholds for ventricular tachycardia and fibrillation, in turn caused by infarction, high serum concentrations

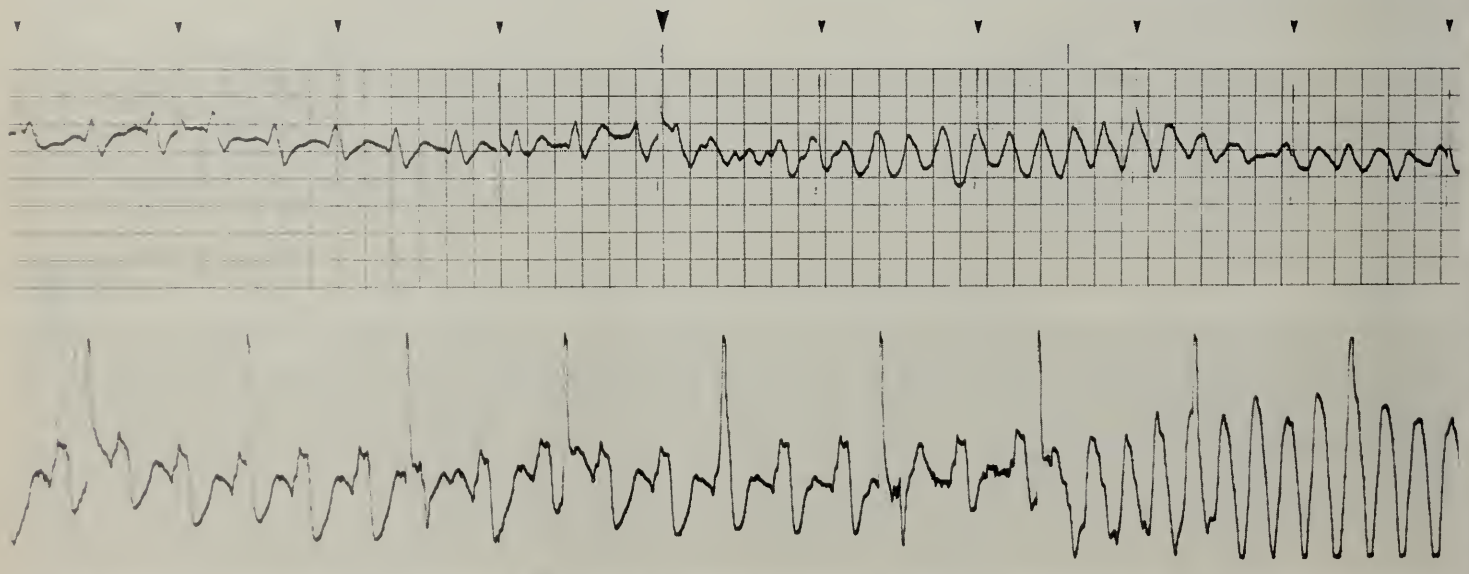

Figure 4.—These modified Lead II rhythm strips were recorded in close temporal proximity. A wide complex tachycardia (probably atrial flutter with 2:1 atrioventricular conduction) is occurring at a rate of 150 per minute. Pacemaker nonsensing is evidenced by the appearance of pacing artifacts at a regular rate of about 50 per minute **(arrows, top strip only).** In the top strip, delivery of a pacing stimulus at the end of the QRS complex **(large arrow)** results in ventricular fibrillation. In the bottom strip, a similarly timed pacing stimulus results in ventricular flutter.

of digoxin,[18-20] metabolic acidosis and probable stress-related sympathetic stimulation. In this connection it is noteworthy that infusions of epinephrine or low doses of isoproterenol and performance of physical exercise, with its attendant sympathetic stimulation, result in measurable, if transient, decreases in pacing threshold in humans.[13] The decreases in pacing threshold due to sympathetic stimulation could make a patient more vulnerable to pacemaker-induced rhythm disturbances.

Chest wall stimulation resulting in pacemaker inhibition was a lifesaving maneuver in this patient: it abolished his pacemaker-induced ventricular tachycardia and fibrillation. While use of chest wall stimulation in the setting of acute myocardial infarction with competitive rhythms has been reported,[4] its use in preventing life-threatening dysrhythmias has not been emphasized. As the technique of chest wall stimulation is easily and usually rapidly accomplished, familiarity with it by physicians managing patients with pacemakers is necessary. The prolonged use of suction cup electrodes did not pose any problems in our patient. The electrodes were secured to the chest with ample amounts of tape so as to avoid their falling off. Bleeding into the skin was not observed, and no discomfort was produced by the chest wall stimuli at the current strength used. If surface electrode stability using suction cup or paste-on skin electrodes is marginal, steel suture wires or small gauge metal needles introduced subcutaneously may be used instead and connected to the external pacemaker generator by alligator cables; these materials may be particularly useful if prolonged chest wall stimulation is anticipated.

Chest wall stimulation to inhibit implanted unipolar pacemaker generators is generally somewhat easier to accomplish than for bipolar pulse generators since in unipolar systems the pacemaker generator itself serves as the anode, resulting in wide separation between anode and cathode. In order to inhibit bipolar pacemaker generators, the surface or subcutaneous electrodes must be placed over the presumed position of two closely spaced intracardiac electrodes having an interelectrode distance of 1 to 2 cm. The surface electrodes are generally placed about 5 to 7 cm apart, to the right and left of the lower sternum, approximating the assumed location of the tip of the electrode catheter at the apex of the right ventricle. Despite the considerable time that must occasionally be devoted to achieving optimum location of the surface electrodes in patients with bipolar pacemakers, inhibition may not be achieved. Under these circumstances, consideration must be given to their removal.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgement before publication.

Senior Licensed Physicians in Utah

To the Editor: A study was undertaken to construct a profile of senior (age 65 or older) licensed physicians in Utah. According to Utah's State Department of Business Administration, in 1982 there were 195 senior licensed physicians in the state. A mail survey was used to determine whether they still practiced medicine. Practicing physicians were asked to describe their practice and their retirement plans. Retired physicians were asked why they maintained a license. Responses were received from 127 physicians (65 percent). Of these, 79 (62 percent) were still practicing medicine and 48 (38 percent) were retired. Subsequently, 30 of the retired physicians were interviewed.

Most of the 79 practicing senior physicians saw new patients and treated hospital as well as office patients. Of the ten senior physicians who did not see new patients and the nine who did not treat hospital patients, seven were the same persons—equaling only 13 percent of senior practicing physicians. The median working hours per week for senior physicians was 50 hours and the median number of patients seen per week was 70.

According to a literature review, the authors found that upper-class workers, such as physicians, have the highest degree of work satisfaction, and, consequently, maintain the highest degree of commitment to continue to work.[1,2] Thus, the fact that many senior physicians continued to practice medicine was not surprising. Moreover, the majority (60 percent) had no retirement plans.

The Utah data are consistent with an American Medical Association survey that found that when 1,000 physicians were asked when they expected to retire more than a quarter said they were never going to retire from medicine—according to an article in *AMA News* by C. Golin (1977; 20[50]:19-26). In a cynical view of why physicians seem reluctant to retire, Rogers concluded as follows

> The really important reason, which doctors are loathe to admit, is that they know little outside their own worlds. Doctors as a class are poorly educated except in medicine.[3]

Whether Rogers' cynical view is justified or not, the fact is that many physicians who do retire, do so because of illness or disability rather than because they planned a post-medical practice way of life.

TABLE 1.—*Reasons Given for Maintaining License*
N=48

Reason	*Number**	*Percent**
License not yet expired since retirement	6	13
To treat family and/or friends	23	48
For possible return to work	15	31
Personal pride and satisfaction	18	38
For motivation to continue CME	6	13
For charity work	3	6
For emergency situations	5	10
Other	4	8

*Numbers add up to more than 48 and the percentage is greater than 100 because many physicians mentioned more than one reason for maintaining a license.

With regard to the 48 retired senior physicians who maintained a license, their mean age at the time of the survey was 73.3 years and at their time of retirement was 69.0 years. Seven of the retired physicians had retired before the age of 65; five of these did so for health reasons.

In Table 1, types of reasons by retired physicians for keeping a license are shown. The most commonly given reason was to be able to legally treat and prescribe for family and friends. The second most commonly given type of reason was for what we termed "personal pride and satisfaction." However, it was cited by three quarters of the 30 physicians who were interviewed. Feelings of personal pride and satisfaction emerged, in particular, during the interviews perhaps because respondents found it easier to talk about rather than write about their personal feelings. A typical statement made by one physician in the survey was that "I really hate to divorce myself from medicine completely. I think keeping a license for many of us oldsters is like keeping some kind of umbilical cord that connects us to medicine somehow."

This study raises issues for both practicing and retired physicians. For senior practicing physicians, their reluctance to retire or make plans for retirement should interest continuing medical education planners in preparing (1) programs that would assist senior physicians in making career plans and (2) programs that would be relevant to their practices. For retired physicians, their desire to maintain a license should interest state

licensing boards in terms of their requirements. Perhaps new categories of medical licenses are needed to designate honorary status or limited practice.

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Department of Family and Community Medicine
BRADFORD BURTON
Second-Year Medical Student
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Salt Lake City

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3. Rogers P: Why doctors seldom retire. Southwest Med 1970 Apr; 51: 82-83

Controversy Over February Symposium

To the Editor: I find it preposterous that a publication pretending to be a scientific journal would devote the first six articles of an issue[1] to political propaganda. You have been duped by the KGB—read the *Reader's Digest* article on the "peace" movement!

Please delete my name from your mailing list.

WALTER L. JOHNSON, MD
San Diego

REFERENCE

1. Medical Consequences of Nuclear War Symposium. West J Med Feb; 138:205-226.

* * *

To the Editor: Thanks! Your editorial "The Absurdities of Collective Extinction" and the five articles on the medical consequences of nuclear war made me proud to be a member of the California Medical Association. This problem is overwhelming in its importance and insane in its continued escalation. I'm comforted that this symposium was published, taking the problem out of the "left wing," as "conservative" medicine helps to show it all is far beyond politics.

Thanks for your courage in printing this.

PAUL KAUFMANN, MD
San Francisco

* * *

To the Editor: Henry Kissinger has severely criticized the tendency to treat foreign policy as a "subdivision of psychiatry." I was therefore dismayed to see that the extensive space given to discussion of "medical consequences of nuclear war" has now made the weighty problems of international relations a province of the field of preventive medicine as well. The implication of much of this writing is that physicians, because of their training (or perhaps because they wear white coats), have some sort of special sensitivity that political leaders and generals lack. To my way of thinking, this represents a combination of naivete and conceit. The papers represented essentially political opinions wrapped up in a scientific package; particularly bizarre were many of Dr Lipton's implications that fear of nuclear war is a cause of teenage mischief and drug abuse, among other things.

The Physicians for Social Responsibility is an essentially populist organization that perceives *all* governments as *equally* objectionable, all unresponsive to the yearning of "decent people." Perhaps so as not to take sides, this organization has not spoken out against consistent violations by the Soviet Union of arms control agreements, particularly with respect to the use of chemical-biological agents. Will there be a symposium on the horribly debilitating effects of biological warfare in the near future? Will there be a symposium on how an attempt to establish a peace movement in the Soviet Union independent of the government was squashed by putting the movement's founder in a KGB-controlled psychiatric hospital?

JOHN HOCHMAN, MD
Encino, California

* * *

To the Editor: Great praise and thanks are due to the editors of the journal for publishing the symposium on the medical consequences of nuclear war in the February 1983 issue. It is a sign of encouragement, and also of the danger of our times, that the physicians' antinuclear movement has grown from ten MDs in New York and Boston to tens of thousands around the world in only four years. I am pleased to see The Western Journal of Medicine joining other prestigious medical journals in presenting this overridingly important formation to the members of our profession.

Equally important as our task, for me at least, has been the unique opportunity to meet so many caring, sensitive and concerned colleagues from all specialties joining together to prevent the unprecedented epidemic of death that nuclear war would loose upon the world. I expect that some of the authors who were part of the journal's symposium will be life-long friends. And I firmly believe that through the combined efforts of all of us, we and our children will indeed have long lives to enjoy.

JOHN M. GOLDENRING, MD, MPH
Research Fellow—Adolescent Medicine
Childrens Hospital of Los Angeles
Los Angeles

* * *

To the Editor: Congratulations on your February 1983 issue in which you bring the medical consequences of nuclear war to the foreground. This topic has to receive top priority. Unless physicians stand together in combating what cannot be called anything but nuclear insanity, discussion of any or all other medical concerns will soon be rendered irrelevant.

HERBERT BAUER, MD
Davis, California

* * *

To the Editor: Heartfelt thanks and congratulations on the *best issue ever* of *WJM* (February).

Maybe we can, with our world-wide colleagues, put an end to the military madness. Copies of this *WJM* should go to President Reagan and *all* members of Congress.

FREDERICK M. EPSTEIN, MD
El Cerrito, California

The Meixner Test

To the Editor: I would like to comment on the "Mushroom-Related Call Data Form,"[1(p288)] in the October article, *"Amanita phalloides*-Type Mushroom Poisoning," which gives directions for performing a Meixner test. As one of the authors of the reference cited (number 9),[1(p289)] I strongly suggest that you change the instruction "add two to three drops of concentrated hydrochloric acid" to "add a single drop of concentrated hydrochloric acid" since it is imperative to use the smallest amount of acid possible. Even two drops will cut down on the detection limit of low amounts of amatoxins such as those found in certain *Lepiota* and possibly *Galerina* spp. Personally, I prefer to use a microhematocrit capillary tube which seems to deliver just about the right amount of acid. Also, I always spot a "control" drop of acid adjacent to the mushroom extract being tested. This is important because some papers may produce color reactions for some unknown reason. Minute quantities of acid are also essential when testing remnants of the food, stool or vomitus. The latter two may contain visible amounts of the toxins when tested within approximately 15 hours after ingestion. Stool and vomitus should be diluted with methanol, centrifuged and filtered. The filtrate can be spotted on newsprint. Methanol will help to extract the toxins.

PAUL P. VERGEER
Director, Toxicology Group
Mycological Society of San Francisco, Inc.
Richmond, California

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* * *

Dr Olson Replies

To the Editor: We appreciate Mr Vergeer's comments regarding the Meixner test, and regret the error in the amount of hydrochloric acid to be used which appeared on the data form.

We would like to remind readers that even if the *test* is truly negative, it does not necessarily rule out *ingestion* of amatoxins. Mixtures of mushrooms may be consumed and the one that is presented for testing may not be the toxic one.

KENT R. OLSON, MD
Clinical Toxicology
San Francisco General Hospital Medical Center

Anaphylaxis Following Zomepirac Ingestion

To the Editor: This is a report concerning anaphylaxis following the ingestion of zomepirac sodium (Zomax).

In a middle-aged man who was taking antihypertension medications, low back pain developed while he was exercising. Ingestion of a 100 mg tablet of zomepirac was followed in ten minutes by substernal oppression, diaphoresis, fecal and urinary incontinence, collapse, wheezing, cyanosis, pruritus and urticarial rash. The patient said that he had had an uneventful two-week course of zomepirac therapy ten months before. Tests were negative for asthma or aspirin allergy. There was prompt response to administration of saline and steroids, with an uneventful recovery.

There are two cases reported in the literature.[1,2] There have been no reported cases to the Arizona Poison Control Center (personal communication, Dr T. G. Tong, January 4, 1983). A medical director from the manufacturer said he was aware of only a few cases of anaphylaxis (personal communication, Dr J. D. Siegfried, January 5, 1983). A staff person from the Food and Drug Administration stated that there was quite a large number of similar cases but he could not cite a figure (personal communication, Mr R. A. Eaton, Division of Drug Experience, January 5, 1983).

The recent announcement by the manufacturer that there have been more than 1,000 cases of anaphylaxis and five deaths seems to belie the paucity of cases reported in the literature. Perhaps physicians should be more conscientious in reporting such observations more promptly.

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Hoemako Hospital
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Lasègue, Not Laséque

To the Editor: Lasègue, not Laséque.

In the Epitome section of the November 1982 issue, the famous French physician's name was misspelled in two ways, namely with an accent *aigu* instead of an accent *grave* and with a "q" instead of a "g."[1]

Should one trust the contents of a bottle if the label is wrong?

ERNST W. BAUR, MD
Tacoma, Washington

REFERENCE

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The Use of Acronyms

To the Editor: Like Dr Alfred Robinson,[1] I, too, am irritated by the use of acronyms. I have made my complaints to the various publications I receive indicating the confusion it causes and the increased difficulty in trying to digest the articles I read that are "salted" with these acronyms. Please tell me why they are used.

CARL W. KOERPER, MD
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Western Electric
San Leandro, California

REFERENCE

1. Robinson AG: Acronyms in medical papers (Correspondence). West J Med 1982 Sep; 137:251

Editor's Note: We entirely agree with complaints against the use of acronyms in medical journals. In copyediting, *WJM* staff eliminate most of the acronyms originally appearing in accepted manuscripts. How-

ever, occasionally a term being replaced is so long or is used so frequently throughout a paper that the decision is made to let the acronym stand and spell it out in an "Abbreviations Used in Text" box at the beginning of the article. Nonetheless, we appreciate it when readers call attention to the overuse of acronyms and let us know that we are slipping into "indigestibility."

—MSMW

Steroid Therapy and the Risk of Gastrointestinal Injury

To the Editor: Pezner and Lipsett[1] suggest that while corticosteroids are highly effective in patients with metastatic disease to the brain, the use of dexamethasone in dosages of 12 mg or more per day increases the risk of peptic ulcer disease (PUD). Major flaws in this study's method make it unreasonable and potentially dangerous to accept this conclusion.

In this series, PUD developed in five patients who received "high dose" steroids; 84 patients also received similar high doses but PUD did not develop. Seventeen patients did not receive at least 12 mg per day, and in none of these patients did PUD develop. These 17 patients make up the control group (unidentified by the authors), on the basis of whose comparison with the other 89 (treatment group) the authors base their conclusions.

It is in general difficult to prove cause-and-effect relationships in retrospective studies, particularly when groups being compared are not shown to be similar in baseline characteristics. If we are to believe that the use of a certain dosage of steroids is the independent variable associated with the development of PUD in these patients, we must first be assured that there are no other independent variables, such as differences in age, type and degree of underlying disease, other modes of treatment and the like. Not only is none of this information clearly available about the two groups in this series, but there is at least the suggestion that patients who received the higher doses had more severe illness than those who did not. We are not told anything about the use of other medications or the presence of other significant diseases in either of the groups in general, but we are told that four of the five patients in whom PUD did develop had seven other plausible causes for this complication, not including their underlying central nervous system disease. Finally, while the authors claim that the so-called relationship between steroid use and PUD was dependent upon the dose of dexamethasone used, "tapering of dexamethasone dosage had been started in two patients before the peptic ulcer disease developed . . . ." (We are not even told whether their total dosages were below 12 mg per day at the time of onset of their symptoms.)

Of even greater concern is the misuse, or rather nonuse, of statistical analysis in this paper. The authors state at the end of their Methods section that statistical significance was tested by the x^2 method, but in fact they do not at any point in the paper make any statistical comparisons. In fact the difference between the treatment and control groups with regard to development of PUD is not statistically significant. Five of 89 is easily seen to represent just *under* 1 in every 17 patients, so the absence of any PUD in the control group of 17 is intuitively well within the realm of chance statistical variation (even if both groups were in fact matched with regard to all variables except steroid use, and if treatment entailed no increased risk of PUD). Not surprisingly, x^2 testing shows the difference between the groups to be far from significant, with a P value of close to 0.5.

There may be some point in reporting a retrospective review of complications seen in a group of patients with brain metastatic disease, most of whom received at least 12 mg per day of dexamethasone therapy; it is irresponsible, on the other hand, to state conclusions that are not only impossible to evaluate because of the incompleteness of the information presented, but which even in the best possible case are not supported by the limited data presented. It is furthermore dangerous to do so when misinterpretation of such data, as in the authors' discussion, might lead some readers to withhold an extremely valuable medication.

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* * *

To the Editor: The fine article by Pezner and Lipsett, "Peptic Ulcer Disease and Other Complications in Patients Receiving Dexamethasone Palliation for Brain Metastasis," discusses the association between corticosteroid therapy and gastrointestinal injury.[1] They also raise important questions regarding the use of prophylactic antacids in patients receiving high doses of dexamethasone and other steroids. I would like to add some comments to their discussion.

Theoretically, corticosteroids have significant ulcerogenic potential. It is unlikely, however, that dexamethasone alone (at doses higher than 12 mg per day) was responsible for the development of peptic ulcers in the five patients described in the study. Three of the five patients were also using unspecified doses of nonsteroidal anti-inflammatory agents (NSAIA's), two patients had thrombocytopenia and one patient had a history of ethanol abuse. These associated factors undoubtedly increase the risk of peptic ulcer disease and gastrointestinal bleeding developing.

Whereas nonsteroidal anti-inflammatory agents have well-documented potential for causing gastrointestinal injury, controversy concerning the association of corticosteroid treatment and peptic ulcer disease remains

unsettled.[2-3] The study by Conn and Blitzer is a retrospective analysis in which the majority of patients received daily corticosteroid therapy at varying doses for up to 365 days; they concluded that steroids are not associated with a higher incidence of peptic ulcer disease. Using a different statistical manipulation, another group of investigators analyzed these same data and concluded, quite differently, that corticosteroids do cause peptic ulcer disease.[3] A review of the literature reveals several major clinical reports that suggest a causal relationship between corticosteroid therapy and gastrointestinal injury.*

Recent experimental studies describe some of the mechanisms underlying gastric-mucosal injury and cytoprotection. Prostaglandins have been found to play an integral role in protecting the stomach against mucosal damage induced by alcohol, steroids and NSAIA's.[4,5] In addition to their inhibitory effects on acid secretion some prostaglandins stimulate bicarbonate secretion, stabilize lysosomal membranes and increase production of mucus. Commonly used steroids and NSAIA's inhibit arachidonic acid metabolism to prevent synthesis of prostaglandins in many tissues, including gastric mucosa. The mechanisms of action and interaction of these drugs have not been precisely elucidated.

In summary, it is highly likely that corticosteroids contribute to the pathogenesis of peptic ulcer disease. Furthermore, prophylactic antacids may be beneficial in patients who require corticosteroids or NSAIA's (or both) for the therapeutic management of acute and chronic illness. It has been shown that peptic ulcers may heal with antacids during continuing anti-inflammatory drug therapy in patients with rheumatoid arthritis. Likewise, preliminary studies indicate that cimetidine, a selective antagonist at H-2 histamine receptor sites, has a protective effect against gastric-mucosal damage induced by steroids and NSAIA's.[6] Perhaps the time has come for controlled clinical studies that examine the effect of prophylactic antacids or cimetidine (or both) on the incidence and severity of peptic ulcer disease in patients who are treated with anti-inflammatory drugs.

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* * *

Drs Pezner and Lipsett Respond

DRS HOFFMAN AND BARAFF correctly point out several limitations inherent in any retrospective review. We doubt that anyone would propose a prospective randomized study in which steroid therapy is withheld from some patients with symptomatic brain metastases. The point of our paper is not that steroid therapy should be withheld from patients with neurological symptoms. Rather, it is that patients should not be maintained on steroids for longer than necessary since they will be put at risk of complications. We recommend that patients with symptomatic brain metastases begin dexamethasone promptly but that the steroids be tapered in dosage as tolerated within one to two weeks after starting radiation therapy. Gradual tapering to discontinuation can usually be accomplished in about two weeks. A few patients will require chronic steroid therapy for symptom relief but the dose should be kept as low as possible. In addition, we recommend that other ulcerogenic agents (such as aspirin-containing products, alcohol) be avoided.

Mr Molina has provided an excellent review of proposed pathophysiological mechanisms of steroid ulcerogenesis. Whether prophylactic use of antacids or cimetidine (or both) will be of value remains unproved. A prospective randomized study might be able to provide an answer. Such a trial, however, would require hundreds of patients to provide a statistically significant answer. It might indeed be an appropriate study for one of the regional or national oncology study groups.

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Topics in Primary Care Medicine

The Alcohol-Withdrawal Syndrome

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"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

—BERNARD LO, MD
STEPHEN J. McPHEE, MD
Series' Editors

The syndrome of alcohol withdrawal is characterized by tremulousness, hallucinations, seizures and delirium following withdrawal from ethanol. The severity of the withdrawal syndrome depends on both the amount and the duration of ethanol consumption. The syndrome can be precipitated at any time during which the blood ethanol concentration decreases. Therefore, not only cessation but a reduction in the intake of ethanol can precipitate the withdrawal syndrome. Some patients consume smaller quantities of ethanol but concurrently take other sedative-hypnotic agents (barbiturates, benzodiazepines) that are cross-tolerant with ethanol. A syndrome similar to ethanol withdrawal can also be precipitated if one of the sedative-hypnotics is withdrawn.

Clinical Presentation

The alcohol-withdrawal syndrome can be divided into four clinical stages. During stage 1 (six to eight hours after the cessation of ethanol intake), signs and symptoms of autonomic hyperactivity predominate. Most patients experience tremulousness and anxiety. On physical examination tachycardia, hypertension, diaphoresis and hyperreflexia are often found. In addition, a patient may be easily startled, and there may be a craving for alcohol or other sedative-hypnotic drugs.

In stage 2 (about 24 hours after ethanol cessation), hallucinations occur and accompany the autonomic hyperactivity of stage 1. The hallucinations are usually auditory or visual but may be tactile, olfactory or mixed.

The hallmark of stage 3 is the appearance of grand mal seizures. The overwhelming majority of patients who have seizures do so within 7 to 48 hours after the cessation of ethanol intake. Most patients will have two to six seizures in a six- to eight-hour course. The seizures are brief and a patient usually has a relatively short postictal period. About 30 percent to 40 percent of untreated patients who have seizures during ethanol withdrawal will go on to have delirium tremens.

Stage 4 of the ethanol-withdrawal syndrome is characterized by autonomic hyperactivity, hallucinations and global confusion (delirium tremens). The occurrence of seizures after the onset of delirium tremens is distinctly unusual. This stage begins some 72 hours after cessation of ethanol intake, but can be seen as late as 14 days. In only about 6 percent of patients who withdraw from alcohol do the symptoms, if untreated, progress to this stage.

It appears that patients who are at greatest risk for delirium tremens developing will have either temperatures above 40°C (104°F) or fluid or electrolyte disturbances. Complications include aspiration, trauma and vascular collapse. Mortality from delirium tremens is still estimated at 15 percent to 25 percent.

Pathophysiology

While no satisfactory pathophysiologic explanation for the alcohol-withdrawal syndrome exists, clinical experience has shown that in patients who are tolerant to "toxic" levels of ethanol some compensatory physiologic mechanism must develop that opposes ethanol's depressant effects. When blood ethanol concentrations begin to decrease, these compensatory mechanisms become unopposed and appear clinically as autonomic hyperexcitability (that is, tremor, hypertension, tachycardia and hyperreflexia). In addition, hypomagnesemia

Refer to: Brown CG: The alcohol-withdrawal syndrome (Topics in Primary Care Medicine). West J Med 1983 Apr; 138:579-581.

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and hypokalemia may be factors in the development of the withdrawal syndrome.

Differential Diagnosis

The tremor of alcohol withdrawal poses little difficulty in determining differential diagnosis, especially when there are other autonomic signs and symptoms and a history of recent cessation of ethanol intake. The tremor of alcohol withdrawal is postural and therefore maximal when a patient's arms are outstretched. It is a fairly rhythmic tremor that oscillates at about six to eight cycles per second and worsens with agitation. Another postural tremor seen in this patient population is asterixis. This occurs with a metabolic encephalopathy (for example, hepatic failure) and is more intermittent and irregular than the tremor of alcohol withdrawal. Cerebellar tremors, which can be seen with alcoholic cerebellar degeneration or as part of Wernicke's syndrome, worsen with movement and abate at rest, and therefore are easily distinguished from postural tremors.

The hallucinations seen during stage 2 of ethanol withdrawal need to be differentiated from alcoholic hallucinosis, an alcohol-related toxic psychosis. The differentiation is made on the basis of time of onset, presence of autonomic signs and symptoms and the type of hallucination. With alcoholic hallucinosis the onset of the hallucination begins within 72 to 96 hours after the cessation of ethanol intake and is not characterized by the presence of autonomic hyperexcitability as occurs in ethanol withdrawal. The hallucinations of alcoholic hallucinosis are usually auditory. In ethanol withdrawal, auditory hallucinations as well as visual, tactile and olfactory hallucinations may occur.

Seizures seen during ethanol withdrawal are classically grand mal and short-lived. As mentioned, most patients have two to six seizures in about an eight-hour time course. A greater number of seizures—or seizures occurring past this time course—should alert a physician to consider other causes.

With the initial presentation of seizures during alcohol withdrawal, the differentiation from idiopathic seizures is at times quite difficult. If electroencephalography can be done, this may aid in the differential diagnosis. In patients with alcohol-withdrawal seizures, an electroencephalogram may show abnormalities during a seizure, but the findings should return to normal shortly following it. In patients with an underlying seizure disorder, electroencephalographic abnormalities are present both during the seizure and after recovery.

Status epilepticus is quite unusual during ethanol withdrawal and should suggest other causes, including withdrawal of short-acting barbiturates and central nervous system infections. Focal seizures seen during ethanol withdrawal suggest an underlying structural lesion such as subdural hematoma, subdural empyema, intracerebral hemorrhage, cerebrovascular disease, arteriovenous malformation or tumor.

The appearance of delirium within the context of the withdrawal syndrome presents little diagnostic challenge. When it is the initial presentation, other disorders should be considered including central nervous system and systemic infections, as well as thyrotoxicosis and hypoglycemia.

In many patients who have chronic alcoholism and who are admitted to hospital for such problems as gastrointestinal bleeding, trauma, pneumonia or hepatic decompensation, signs and symptoms of alcohol withdrawal may develop during their hospital stay. Therefore any alteration in vital signs, mental state or manifestations of seizure activity must be viewed with this in mind.

Treatment

In the early stages of alcohol withdrawal the objectives of treatment should be to allay symptoms and to halt the progression of the withdrawal syndrome. Although reinstitution of alcohol intake is probably one of the most widely used forms of "self-treatment" its short duration of action and the metabolic disturbances that result from its consumption make this an inappropriate treatment modality. Several other sedative-hypnotic agents, which are cross-tolerant with ethanol, are more effective in abating the autonomic hyperactivity and suppressing the hallucinations.

One useful sedative-hypnotic is paraldehyde. It is effective in dosages of 10 ml by mouth every two to three hours. It should not be used intramuscularly because it may cause sterile abscesses, or per rectum because it may also cause a regional proctitis. Although its odor might be considered a detracting factor, this also tends to lower its abuse potential.

Other drugs that may be effective during these early stages include diazepam, chlordiazepoxide and oxazepam. In patients who have hepatic disease or hypoproteinemia, administration of diazepam and chlordiazepoxide must be cautiously regulated because both these drugs have pharmacologically active metabolites that are protein bound. Therefore, in patients being aggressively treated by the administration of these drugs the cumulative effects of the drugs' metabolites on the patients' level of consciousness must be monitored. Oxazepam does not pose this problem as it is metabolized to an inactive form. Because of this, for outpatient management we prefer giving oxazepam in dosages of 15 to 30 mg by mouth four times a day for five days. Phenothiazine and antihistamine ingestion should be avoided. Phenothiazines decrease the seizure threshold, and the acute anticholinergic effects of antihistamines and phenothiazines can confuse the clinical picture.

The treatment of seizures during alcohol withdrawal remains controversial. Patients who present in the early stages of alcohol withdrawal and who have no history of alcohol-withdrawal seizures are treated only with administration of sedative-hypnotics, as mentioned above. In patients with a history of alcohol-withdrawal seizures, one study has shown that prophylactic treatment with administration of sedative doses of chlordiazepoxide (up to 400 mg per day) plus phenytoin, 100

mg by mouth three times a day for five days, may be more effective than giving chlordiazepoxide alone.

In patients who present with alcohol-withdrawal seizures, our policy is to observe the character and frequency of the seizures. Most patients with alcohol-withdrawal seizures have two to six brief seizures in eight hours. If protected from injury and aspiration, they rarely suffer harm. For these reasons we recommend that anticonvulsant medication be withheld unless a patient has more frequent or prolonged seizures, focal seizures or status epilepticus. Focal seizures and status epilepticus require further workup. Long-term therapy with anticonvulsants given for alcohol-withdrawal seizures is not indicated as an underlying seizure focus does not exist.

Patients presenting with delirium tremens often have associated pulmonary and hepatic disease, dehydration and electrolyte disturbances. To treat these patients and search for other underlying disorders, intravenous administration of diazepam is the treatment of choice, with 10 mg given initially followed by 5 mg every five minutes. Once a "calm" state is induced, maintenance treatment with diazepam given by mouth may be instituted at a dosage of 5 to 20 mg every six hours.

Finally, other problems that are commonly associated with alcohol abuse must be sought out and treated in a patient who has the withdrawal syndrome. These include problems with temperature regulation (hyperthermia or hypothermia), head injuries, alcoholic ketoacidosis, gastrointestinal bleeding, pancreatitis, hypoglycemia, thiamine deficiency and electrolyte disturbances such as hypokalemia and hypomagnesemia. Hypertension seen during alcohol withdrawal usually resolves in several days and need not be treated during withdrawal unless the patient is symptomatic or has a preexisting cardiac, renal or vascular disease.

Once the acute abstinence syndrome has been treated, plans for long-term rehabilitation should be initiated. Both drug (for example, disulfiram) and group therapy (Alcoholics Anonymous) have met with varying degrees of success and therefore a treatment regimen must be individualized for each patient.

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Medical Education

The Effect of an Individualized Practice-Based CME Program on Physician Performance and Patient Outcomes

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The Professional Competence Assurance Program (PROCAP) is an individualized educational program that examines physicians' performance in ambulatory practice. It uses medical record review to identify deficiencies in the care process that guides development of the educational intervention. Medical care is reassessed one year later. This program was used with 51 private practitioners to assess the care of 1,229 hypertensive patients. The educational program included a computer printout comparing one physician's performance with that of peers, readings targeted to management problems, and a conference call or group seminar with an expert stressing issues relevant to each physician's performance. Postintervention assessment showed that physicians prescribed beta-blockers ($P<.01$) and vasodilators ($P<.01$) more often. Improvement ($P<.05$) occurred in the control of diastolic blood pressure (≤ 90 mm of mercury) and in several other criteria. These results show that well-designed, individualized continuing medical education addressing specific deficiencies can change physicians' performance and patients' intermediate outcome.

Although formal continuing medical education courses are generally satisfactory experiences for participating physicians, they have been shown to be of limited effectiveness in changing physicians' performance in their practices or in improving patient outcomes.[1] Despite reports that traditional courses do increase medical knowledge, as measured by tests before and after courses, most investigators have not been able to show actual changes in physician behavior as a result of continuing medical education.[1-3]

Tests of medical knowledge and follow-up questionnaires do not adequately evaluate physician performance and patient outcomes. To obtain evidence of performance and not knowledge, previous investigators have developed methods for direct observation[4,5] and the review of medical records.[6-9] In particular, patient care appraisal, or the use of explicit sets of criteria for the review of medical records, has been found to be an effective method for assessing both performance and outcomes.[10-13] The use of patient care appraisal to structure a continuing medical education program in a hospital was first outlined by Williamson[14] and elaborated on by Brown and Uhl[15] and Brown and Fleisher.[16] Sanazaro[13] and others have suggested that this notion could be applied more successfully to ambulatory care, and Putnam[17] has shown patient care appraisal to be an effective continuing education tool when the physician has been involved in generating the criteria for the appraisal.

Using these concepts, we have developed a Professional Competence Assurance Program (PROCAP) which employs patient care appraisal to assess the performance of individual physicians in their offices, links an individually tailored educational program to the assessment and evaluates physician performance and patient physiologic outcomes following the educational intervention. We applied this program to the performance of 51 physicians in the ambulatory care of 1,229 pa-

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tients with hypertension. Our results show that there was a significant improvement in patient outcomes and physician performance following our educational program.

Methods

In this study, hypertension was selected for practice review because of its frequency as a diagnosis, the availability of a sufficient number of patients in each practice, the general agreement regarding adequate treatment[18] and the ease of measuring outcome.

Criteria Development

Members of the academic faculty at the University of California, San Francisco, who are expert in the field of hypertension developed a list of ideal criteria for the diagnosis and treatment of hypertension. They were asked to select criteria without respect to time, cost, availability of resources or patient acceptability. The project steering committee was formed, consisting of faculty, practitioners not in the study group, and representatives of internal medicine and family practice professional societies. They discussed the criteria and simplified the list to include only essential criteria likely to be identifiable in an office medical record and likely to make a difference in patient care.[13] Criteria affecting only a small subset of patients (such as those with renovascular hypertension) and those involving hospital admission (such as arteriography or renin studies) were excluded. Over the next year the steering committee met several times to further modify the criteria, which were then tested in small pilot studies of the office records of 18 physicians.

The criteria used in this study appear in Table 1. Those involving diagnosis, treatment and education are called process criteria. The outcome criteria are based on blood pressure measurements. In this study, a diastolic blood pressure of 90 mm of mercury or lower was considered the criterion for successful control of blood pressure.

TABLE 1.—*Baseline Adherence to Criteria Compared With Reassessment Levels in Treatment of 953 Patients From 48 Physicians' Practices*

	Baseline percent		*Reassessment percent*
History			
Renal signs and symptoms	55	*	60
Neurological signs and symptoms	82	*	87
Risk factors and family history	83		86
Physical examination			
Funduscopic examination	62	*	57
Laboratory			
Urine analysis for protein	77		76
Urine analysis for casts	74		75
Creatinine or blood urea nitrogen	84		82
Therapy			
Use of medications			
Beta-blockers	25.8 (246)	*	30.3 (289)
Vasodilators	9.6 (92)	*	13.7 (131)
Reserpine	9.1 (87)	*	5.9 (56)
Methyldopa	14.2 (135)		13.1 (125)
Measurement of blood pressure in multiple positions	21	*	46
Patient education			
Concerning disease	58	*	70
Concerning diet	61	*	67
Outcome			
Normotensive $\leq$90 mm Hg	74	*	81

*=Significant ($P<.05$). Only criteria with less than 85 percent compliance are listed.

Physician Population

A total of 750 internists and family physicians in the San Francisco Bay Area were sent informative brochures and letters of invitation to participate in the study. Of these, 51 agreed to participate, and 48 completed both the baseline audit and the reassessment 12 months later. All participating physicians received the educational intervention.

A majority of the physicians were white men, 6 percent were women and 12 percent were members of minority groups. Their average age was 49.5, with a range of 32 to 71 years, and 70 percent were board certified. Of the physicians 43 percent were general internists, 14 percent were family practitioners and the remainder were internists with subspecialties. Two thirds of the physicians were in full-time office practice. Some of the group were clinical faculty members at our medical school or affiliated with urban or small suburban hospitals.

Individual Practice Review

Once the physicians had been selected to participate in the study, they were visited in their offices by a physician representative of the PROCAP team and by the project coordinator. The PROCAP physician reviewed both the ideal and the essential hypertension criteria. The participating physicians were asked whether the list of essential criteria conformed to their usual practice and whether they had any objections to any of them. They were encouraged to set personal standards of compliance with them. The purpose of this consultation was to make the participating physicians aware of the objectives of the study and to provide justification for the essential criteria. In this respect the consultation was considered to be the first phase of the educational intervention.

At the same time that the physician-consultant was conferring with the physician-participant, the project coordinator (T.E.A.) was conducting a survey of office procedures related to patient care. She gathered data about the nature of the practice, characteristics of the office staff, availability of patient educational material, use of paramedical personnel for patient care and organization of medical records. This information was used to design educational materials, but changes in these practice procedures are not reported in this study. At

the close of this preliminary consultation and survey, arrangements were made for the record review to take place within one week.

Medical Record Review

For the medical record review, each physician in the study selected 25 patients currently under care for hypertension. Practitioners were asked to select patients as objectively as possible. The preferred method was to keep a prospective list of hypertensive patients. Alternative methods included the following: referring to computer indexes of diagnoses, scanning appointment books to select consecutive patients with hypertension, searching "superbills" for diagnostic codes, or extracting cases from a physician profile diary of 100 consecutive patient visits.[19] Physician memory alone was not an acceptable method of selection. Selected patients were less than 80 years old, had a diastolic blood pressure greater than 90 mm of mercury then or at some point during their care with this physician (six months or longer) and had no life-threatening comorbidity.

Data were obtained from the medical records by two medical record abstractors who were trained by the project coordinator. Detailed written guidelines were developed for their use including a glossary of terminology and abbreviations, lists of all antihypertensive medications in current use, the type of specific information to be extracted from laboratory data and the expected location of desired information in the medical records. To ensure interobserver reliability, the project coordinator reabstracted some of the medical records periodically throughout the study (the overall r value was .92).

Once 25 patients had been identified, their records for the previous two years were reviewed by the medical record abstractors who recorded all data relevant to the essential criteria. In addition, data regarding blood pressure, medication and dosage for the three visits before the record review were abstracted and coded for computer entry. To ensure confidentiality each patient was given an identifying code and no patients' names or records were removed from the physicians' offices. Two abstractors were able to obtain these data for 25 patients in one working day.

Analysis of Data

The data were then entered into a computer using an interactive program developed specifically for this study. Computer analysis of the data generated a summary printout (Figure 1) that showed compliance with each process criterion for each physician and for the entire peer group. The computer also analyzed outcome data and reported them as a percentage of patients, in each practice and cumulatively, whose hypertension had been controlled (diastolic blood pressure $\leq$90 mm of mercury). These data constituted the baseline assessment. In addition, a computer printout displayed for each patient the medication and dosages, the blood pressure measurements and complicating factors for the three visits before the practice review.

Education

The educational phase consisted of three parts: the printout from the medical record review, the telephone conference call and the supplemental educational packet. The physicians received a summary printout of the baseline data described above. This summary data was utilized by the individual physician to review patient care and by the PROCAP faculty educator. Included with this report were journal articles appropriate to the problems evidenced in the record assessment review.

Telephone Conference Calls. The participants received follow-up consultation by participating in an hour-long telephone conference call[20] or small group meeting. Each session was led by one or two faculty consultants who are authorities on the treatment of hypertension. The objectives of the consultations were to provide feedback on the particular deficiencies present in the studies of group members and to answer questions.

Before the call or meeting, the consultant was given information about the participants. This included a summary sheet displaying each participant's compliance with criteria as compared with the peer group's and the individual patient treatment abstracts. Another summary contained a table with information about members of the group obtained from the survey of office procedures: age, specialty, type of practice, available patient educational materials, use of nursing and paramedical personnel, and the quality of their medical records. For each physician the faculty received a brief statement highlighting problems evident from the record review, such as noting that the physician did not use the newer drugs or used *qid* doses of medication excessively.

The physicians under study were divided into three groups based on the percentage of their patients whose blood pressure was under control. To individualize the conference calls, an effort was made to group physicians with similar study results together and not to mix physicians with extremely high or low performance. This was done to improve the satisfaction of the more sophisticated physicians and to allow the consultant to focus the teaching at the appropriate level. Thus two calls were geared to physicians with high performance, two to those who were average or above and the remaining five were for average or lower performance. In all, 31 physicians, in groups of three to five, participated in conference calls; the remainder attended one of two group meetings except for a few who, due to scheduling problems, had briefer individual telephone consultation. Care was taken to preserve patient and physician anonymity in these discussions.

In many of the calls and in the group meetings, the following were recurrent topics: beta-blocker drugs, especially the newer ones; the value of metaprolol (cardioselective) versus propranolol (nonselective); selection of thiazides; the negative side effects of clonidine, and the use of potassium supplements. Other nonpharmaceutic subjects included the need for salt restriction in the diet, the usefulness of home blood

pressure measurement, the need to document renal problems and the status of the fundi.

Supplemental Educational Packets. As part of the educational program, three packets were prepared. The first, medical record material, was designed to meet deficiencies that were identified in the survey of office procedures. It included preprinted history and physical forms, problem lists and hypertension flow sheets. A second packet addressed cost containment issues, namely blood pressure monitoring by paraprofessionals and the *1980 Redbook* costs of many hypertensive medications. The third packet contained abstracts of two articles that report improved blood pressure levels in patients who have had educational programs. A list of reading materials for patients and a summary of weight reduction programs available in the community were included as well.

Reassessment

Twelve months after the baseline review, a follow-up was conducted in 48 physicians' offices on 953 of the original patients. There were 247 patients who were not evaluable, and so were dropped from the matched sample. These were accounted for by the 74 patients of the physicians who declined reassessment, 133 patients who had no subsequent visits, 10 patients who died and 20 patients whose charts could not be retrieved because the code was misplaced. For the remaining

	1 MD		51 MD's
Number of Patients	25		1229
ESSENTIAL CRITERIA	%		%
HISTORY (past 2 yr)			
Blood Pressure Readings	100		100
Cardio-Vascular Signs and Symptoms	100		95
Renal Signs and Symptoms	20	<<	54
Neurological Signs and Symptoms (CVI)	68		81
Report of Risk Factors and Family History	64	<<	82
JUSTIFICATION OF DIAGNOSIS			
Initial BP reported two times pre Rx, or initial diastolic >= 120	83 /6 *		85 /544 *
PHYSICAL EXAM (past 2 yr)			
A Report of Funduscopic Exam	40	<<	62
Heart Exam	100		95
LABORATORY TESTS (past 2 yr)			
U/A for Protein	60	<<	78
U/A for Casts	44	<<	72
Creatinine or BUN	84		85
THERAPY			
All hypertensive meds listed with dose and freq	84		92
If on meds, BP recorded standing/lying or multiple positions (last 3 visits)	0 /24 *	<<	21 /1129 *
EDUCATION			
Disease:	44		57
Need for Compliance	32		32
Complications	0		7
Adverse Effects of Medications	16	<<	41
Diet:	48		59
Lower Salt Intake	20		30
Weight Reduction	36		47
OUTCOME Most Recent Visit - DIASTOLIC			
Normotensive <= 90	60		73
Trending Down	4		6
Stable or Not Trending Down	36		21
> 100	20	>>	6

* indicates data available for n patients.
<< or >> indicates significant percentage difference between adjacent columns (p < .05)

Figure 1.—Sample computer printout for one physician at baseline review. At left are essential criteria used for record review. At right is percent of one physician's patients as compared to percent of all physicians' patients.

TABLE 2.—*Impact of Educational Intervention on 48 Physicians Grouped According to Performance*
COMPARISON OF BASELINE REVIEW AND REASSESSMENT (F/U)

	16 MDs with lowest portion of controlled patients (N=316 Patients)			*16 MDs with middle portion of controlled patients (N=321 Patients)*			*16 MDs with highest portion of controlled patients (N=316 Patients)*		
	Baseline percent		*F/U percent*	*Baseline percent*		*F/U percent*	*Baseline percent*		*F/U percent*
Diastolic outcome ≤90 mm Hg	61	*	72	72	*	82	88	NS	88
Blood pressure in multiple positions .	19	*	51	22	*	43	24	*	52
Patient education									
Drug regimen compliance	36	*	47	31	*	41	31	*	39
Medication side effects	37	*	48	44	*	54	47	*	58
Low sodium diet	22	*	30	32	NS	37	38	*	47

*=Significant ($P<.05$), NS=not significant.

patients, records were reviewed for compliance with the criteria over the 12-month period; for the three most recent visits, records were again abstracted for blood pressure, medication and dosage; data were analyzed in a fashion similar to the baseline review and a computer report was generated displaying baseline and follow-up data and comparing individual and peer data. The data were subjected to statistical analysis using chi square.

In approximately half of the practices, a congruent patient survey was conducted simultaneous to the medical record review. The patient survey requested information regarding knowledge of the disease, medications, appropriate diet, compliance with the physician's instruction and satisfaction with the care process. The results will be reported in a subsequent article.

Evaluation

Throughout the study, data were collected regarding feasibility of the project, acceptability to the physicians and costs. When the project was completed, all participating physicians were asked to answer a questionnaire evaluating the educational components and the acceptability of the PROCAP process as a continuing medical education program. The questionnaire sought also to determine the level of disruption of office routine and the physicians' willingness to pay for future PROCAP studies.

Results

Table 1 compares compliance with criteria for the treatment of the patients whose records were reviewed initially and reassessed after the educational intervention. Only process criteria for which initial compliance was found in less than 85 percent of the total number of records are included in the table. Outcomes as measured by the proportion of patients with a diastolic blood pressure of 90 mm of mercury or less improved significantly from 74 percent of patients at baseline to 81 percent at reassessment. Average diastolic blood pressure of uncontrolled patients at baseline was 99 mm of mercury. At reassessment the same patients' blood pressure had been lowered to an average value of 90 mm. The statistically significant ($P<.05$) changes are starred. Of the process criteria, taking blood pressure readings with patients in multiple positions, an item stressed in the educational offerings, more than doubled from 21 percent to 46 percent.

The therapy section of Table 1 shows changes from baseline record review to reassessment in the use of medications. There was a statistically significant increase in the use of beta-blockers and vasodilators, and a statistically significant decrease in the use of reserpine. The population of physicians using beta-blockers and vasodilators more effectively at reassessment were those whose patients were better controlled.

The results of analysis of data according to the three performance groups into which the participating physicians were divided are shown in Table 2. The highest third of physicians showed no change in patient outcomes on follow-up. The middle and low groups showed statistically significant improvement in the outcomes of their patients. Several of the practices having the lowest proportion of patients with adequately controlled diastolic blood pressures showed large improvements in blood pressure readings after the individualized educational program. All three groups showed statistically significant improvements in adherence to process criteria such as recording blood pressure in multiple positions and in patient education.

Results of the evaluation of PROCAP by the participating physicians showed that the process was generally acceptable. The telephone conference calls and the small group meetings were rated by 83 percent of participants as good or excellent. The hypertension educational materials were thought to be good or excellent by 64 percent of respondents. The medical record and patient educational materials were found useful by more than 40 percent of the physicians. Importantly, 89 percent felt that there was minimal or no disruption of office routine by the chart review process. Approximately half of the physicians would be willing to pay for such studies in the future.

An analysis was carried out using the direct operating cost data for personnel (faculty, abstractor and analyst), travel to the office (three trips), computer expenses and telephone conference call. A decrease in cost per physician occurred as staff became more efficient in ab-

stracting and processing the data: for the first 16 practices, $452; the second 16 practices, $383, and the last 16 practices, $314.

Discussion

The results of this study show an improvement in important aspects of the care process for patients with hypertension and in the control of the patients' blood pressure after an educational intervention. This study is one of the first studies to show a change in physician performance in the ambulatory setting (private practice) after a continuing medical education program constructed to address specific deficiencies in care discovered by a review of medical records.

Our findings differ from those of Sibley and co-workers[2] who recently reported variable change in physician performance after a randomized, controlled trial of non-individualized continuing medical education. Although Sibley's study assessed performance before and after an educational intervention, their program consisted of packets of materials on topics selected by physicians in the study and not directly targeted to the findings of the assessment. Our educational intervention, on the other hand, was tailored to meet the needs of individual physicians as identified by the medical record review and provided direct interaction with faculty consultants. Although Sibley's study utilized a control group (eight physicians) who did not receive the intervention, and although their participants were randomly selected, our results, based on a greater number of episodes of care (7,546) and a larger number of physicians, strongly suggest that a more highly individualized intervention could lead to improved physician performance and patient outcome.

A recent review of the literature[21] cited eight studies as evidence of a positive effect of continuing medical education on physician performance, but most of these studies used questionnaires following traditional continuing medical education courses to determine whether physicians had applied what they learned or conducted medical record review in a hospital setting. Although the limitations of the use of data from the medical record are well-known,[7-9,20] there can be no doubt that records of blood pressure levels, medication data and the recording of care given are more objective evidence of physician performance and patient outcomes than self-reporting by physicians.

Our study therefore must be seen as an important step forward in developing and implementing a methodology for designing and assessing programs of continuing medical education. Although the improvement in blood pressure outcomes cannot be causally attributed to the educational intervention, we believe that the increased use of beta-blockers and vasodilators and the decreased use of reserpine, as well as improved patient education regarding compliance with drug regimens and low salt diet, were probably the most influential factors.

Our educational program addressed these issues directly. In the telephone conferences and small group discussions, our consultants focused on them as related to the specific patient care situations of the participating physicians.

The preassessment consultations with the participating physicians influenced the participants to be more receptive to later educational intervention. In these consultations, the ideal and essential criteria for the treatment of hypertension were discussed, and the physicians were aided in establishing their own compliance with the criteria. In addition, informal feedback from participating physicians suggests that the printout comparing individual and peer data for compliance to criteria and displaying each patient's treatment record was a powerful tool in helping participants to pinpoint both strengths and deficiencies of care.[23] Because of its ability to focus on individual physician concerns, we felt that the small group conference call or seminar was the most effective aspect of our educational program.[20]

Another encouraging result of our study has been its acceptability to the participating physicians. We found that a staff of two record abstractors could review 25 records in one day. Most of the participating physicians concurred that the record review process was not disruptive, and a large number (50 percent) were sufficiently pleased with PROCAP that they said they would be willing to pay for such studies in the future. This consumer acceptability, in conjunction with the program's effectiveness, indicates that PROCAP may be a valuable component of a physician's overall CME program.

PROCAP may be generalized to other diagnoses and to other communities whose physicians wish to critically study their practice performance. This type of CME should be conducted in concert with a medical school, whose faculty resources would be necessary to provide meaningful education to large numbers of physicians. The costs as reported are relatively high and could be substantially reduced by streamlining the process, which was not possible when conducting the research project.

Some of the problems in conducting CME research include the difficulties in applying the scientific method to the real world of the practice of medicine containing its constraints of time, its motivations and its variances in office environments. Although the selection of physicians' names can be random, the participants will invariably be self-selected. A control group is feasible but difficult in view of the busy schedule of practitioners and their reluctance to participate in a program not directly beneficial to them.

In summary, we assessed the care of hypertensive patients using patient care appraisal and targeted an individually tailored educational program to identified deficiencies. Our reassessment showed statistically significant improvement in the control of blood pressure and in several aspects of the care process. These findings suggest that a continuing medical education program that is individualized can be effective in changing physician performance.

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Medical Practice Questions

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Barbiturate Coma

QUESTION:

Is barbiturate coma a clinically proved modality or is it investigational?

OPINION:

In the opinion of the Scientific Advisory Panels on Anesthesiology, Neurology and Neurosurgery, the use of barbiturate coma continues to be an investigational tool in the management of insult to the brain by cerebral ischemia. It can be considered acceptable clinical treatment for head injuries in certain centers for well-selected patients. There is evidence that the treatment is effective in reducing intracranial pressure (refractory to conventional therapy) or avoiding intracranial hypertension. However, whether this results in increased survival and improved quality of life remains to be proved. The scientific rationale for the use of barbiturate coma in brain protection must await extensive clinical investigation and basic science studies before it is established practice for other conditions.

Because barbiturate coma is a sophisticated technique that carries significant morbidity, it should not be employed indiscriminately. Barbiturate coma for head injuries is permissible on a limited basis where definite criteria for proper patient selection have been established, where there are established criteria for the discontinuation of treatment, where there is present a knowledgeable team including physicians competent in neuro-pharmacology and a knowledgeable supportive nursing team operating under definitive protocol and only in facilities where an appropriate intensive care unit is available for proper monitoring, including measurement of intracranial pressure. Barbiturate coma for the treatment of head injuries should not be employed unless these requirements can be fulfilled.

Barbiturate coma for the treatment of conditions not cited above is not established practice and should be used only under an investigational protocol.

Information

Nonneoplastic Disorders of the Parotid Gland

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A wide variety of conditions may be responsible for enlargement of the parotid salivary gland. When confronted with a patient who has parotid enlargement, the initial step is to decide whether this represents a discrete tumor mass or a diffuse swelling of the gland. If a discrete tumor mass is present, treatment is relatively straightforward and usually involves surgical excision. When a diffuse or bilateral enlargement exists, there are many diagnostic possibilities.

The differential diagnosis of such a disorder requires a systematic evaluation of both the salivary glands and the general medical condition of the patient. The nonneoplastic causes of parotid gland enlargement can be broken down into several major types: infectious, systemic and secondary metabolic causes, drug reactions, local causes and miscellaneous (Table 1). These can be broken down further into those conditions affecting either children or adults.

The various causes of parotid enlargement are herein reviewed, and most of the discussion will concern the diagnosis and treatment of the autoimmune class of diseases. It is this group that generally causes the greatest problems both in diagnosis and treatment.

When a patient with parotid swelling is first seen, the most important factor in narrowing down the diagnostic possibilities is getting a complete history. The duration of symptoms and history of pain, fever, swelling with meals, purulent drainage and associated systemic symptoms are obviously critical factors in deciding what initial tests are indicated. Laboratory and radiologic studies are often helpful and will be discussed under specific disease entities, as will various treatment modalities.

Childhood Disorders of the Parotid

Inflammatory disorders in children are divided into viral and nonviral categories, with mumps being the most common cause of parotid swelling in children.

Mumps is an acute, contagious, generalized viral disease that presents as a painful enlargement of the parotid glands. It is spread by airborne droplets of infected saliva. The incubation period is two to three weeks after exposure and its onset is characterized by pain and swelling of one or both parotid glands, which progresses rapidly in two to three days. Local discomfort is exacerbated by stimulation of the gland. A myxovirus can be identified from a specimen of the saliva as long as six days before and up to nine days after the appearance of swelling.[1-3] Other symptoms include fever, myalgia, malaise and headache, which generally last three to seven days. The parotid is the salivary gland involved in 85 percent of the cases. Diagnosis is usually made from clinical findings but viral cultures and serologic tests can be done. A test for serum antibodies to mumps antigens S and V that results in a titer greater than 1:192 indicates recent infection. Laboratory findings are otherwise nonspecific, except for a mild leukopenia. Most mumps infections occur in children and give a lifelong immunity.

Other viral agents causing parotitis have also been identified and produce a clinical course similar to mumps. Parainfluenza viruses 1 and 3, Coxsackie virus A, echovirus and choriomeningitis virus may all cause a parotitis similar to mumps.[2,3]

Bacterial sialadenitis is relatively rare in children and causes symptoms similar to mumps. It may occur either unilaterally or bilaterally. The only initial clinical features differentiating it from a viral source are the presence of purulent salivary secretions and possibly a leukocytosis. Neonatal suppurative parotitis has been described as a separate clinical entity usually occurring between the ages of 7 and 14 days.[2,4] It is usually preceded by a systemic illness that results in dehydration. In this age group, abscess formation is more prevalent, with 20 percent of reported cases requiring external drainage.[2] Bacteria found in these cases are generally *Staphylococcus aureus* (60 percent), with *Escherichia coli, Pseudomonas, Pneumococcus* and *Streptococcus viridans* also being found. The predilection of the parotid gland for these infections is felt to be due to several factors. The slower flow rate of the parotid with the length of Stensen's duct increases the chance for stasis and ascending infections. Additionally, the composition of parotid saliva (the parotid being entirely a serous gland) is a factor because it lacks the bacteriostatic properties found in the mucus-containing secretions of the submandibular and sublingual glands.[2,5]

Chronic recurrent sialadenitis represents the second most common salivary gland disease of childhood. It can occur throughout childhood but is more common in children less than 10 years of age, with the majority being 5 years old or younger.[5] It occurs in one or both glands equally. It usually presents as an acute swelling of the gland that is painful. Unlike acute suppurative parotitis, there is no surrounding erythema of Stensen's duct and only mild if any systemic signs of infection. Laboratory studies may show a mildly raised leukocyte

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ABBREVIATIONS USED IN TEXT

Ig=immunoglobulin
SS-A=nonorgan specific-specific antibody A
SS-B=nonorgan specific-specific antibody B

count, with an increase in the serum total protein due to a rise in the γ-globulin fraction. The swelling lasts from days to weeks and gradually resolves. The secretions from Stensen's duct are often thick and flocculent. *S viridans* is frequently found in cultures. The diagnosis can be suspected by the characteristic clinical course and confirmed by sialography showing sialectasia.[2,5]

Konno[5] studied 52 cases of recurrent parotitis in children using the findings of sialography, biopsy, antibody titers, measured immunoglobulins and long-term outcomes. He found punctate shadows on sialography films in 45 of 52 cases. When these were classified according to number and size throughout the gland, it was found that those patients in whom extensive changes were noted on sialography had experienced frequent recurrences of the swelling and also were younger at onset of symptoms. In 21 cases of unilateral swelling, bilateral sialography was done. In 22 of 27 Konno found changes in both glands, though they were generally less severe in the side without clinical symptoms. Additionally, sialography was done on 18 siblings in 15 cases of recurrent parotitis. He found mild sialectatic changes in 6 of the 18 but stated that in all of these cases in which siblings were studied severe changes were seen on sialograms.[5] Small parotid biopsy specimens were obtained for study in 13 patients. Histopathologic examination of the specimens showed cystic cavities surrounded by small round cell infiltrates with lymphoid follicle formation. The cystic cavities were felt to be constructed from proliferation of the epithelium of the peripheral portion of the interlobular duct or central portions of the intralobular duct with dilation of its lumen.[5]

Immunologic studies comparing serum immunoglobulin (Ig) A, IgG and IgM in 31 patients and 33 controls showed a statistically significant increase only in the IgM fraction in the 3- to 5-year-old age group, as compared with controls. No other statistically significant differences immunologically were found in the patients studied. Long-term follow-up was done on 35 patients who were observed for between 8 and 11 years. Parotid swelling disappeared completely in 21, with 13 patients showing pronounced improvement. Those who did not have sialographic changes initially did better than those with such changes. Follow-up sialography was done on nine patients who had had sialectasia initially; in two, findings had returned to normal, and in six others pronounced improvement of the ductal pattern was seen. One patient who had not improved clinically also showed worsening of the results of his sialography, with conversion into large cystic cavities.[5]

The cause of this disorder is not known. Possible factors include a mild chronic bacterial parotitis due to *S viridans,* which has been isolated from secretions in several series. A hereditary or allergic predisposition has also been considered.[3,6] The possibility of recurrent viral infections was also investigated by measuring—during the acute and convalescent phases—titers to mumps and nine other viruses. Konno[5] found no consistent relationship of the titers with exacerbations of the disease. Findings on examination of the biopsy specimen and sialography are similar to those in Sjögren's disease and this may represent a manifestation of an autoimmune disorder.

Based on their study and long-term follow-up, Konno felt physiologic immaturity of the immune system might play a role in the cause and recurrent nature of the disease. The disease generally resolves or at least abates with age, but in rare instances may progress into adulthood.[2,5]

Sjögren's disease in children is rare, with 21 cases reported in the literature. Its manifestations are similar to that in adults, which will be discussed later.[7] An unusual cause of recurrent parotitis has been reported

TABLE 1.—*Nonneoplastic Causes of Enlargement of the Salivary Glands**

- Inflammatory
  - Acute (specific)
    - Viral (mumps, Coxsackie virus A, echovirus, and lymphocytic choriomeningitis)
    - Bacterial (staphylococcal, streptococcal, pneumococcal, Gram-negative)
    - Acute suppurative of infancy
    - Postsurgical
    - Terminal debilitation
  - Chronic (specific)
    - Tuberculosis
    - Actinomycosis, and the like
    - ?Sarcoidosis
  - 'Recurrent subacute' and chronic recurrent
    - Self-limited
    - Progressive
    - Lymphoepithelial lesion and Sjögren's syndrome
- Systemic and Secondary Metabolic
  - Obesity, hypertension, diabetes mellitus
  - Malnutrition and associated deficiencies (protein, vitamins)
  - Alcoholism and alcoholic liver disease
- 'Hypersensitivity' and Drug Idiosyncrasy
- Local (Salivary Gland) Disturbances
  - Sialolithiasis
  - Sialoangiectasis
  - Trauma, foreign body, fistula
  - Parotid lymphadenopathy
  - Cysts, mucocele and ranula
  - Local duct obstructions (mucous plugs, congenital)
- Miscellaneous
  - Pneumoparotitis
  - Psychogenic
  - Functional overactivity
  - Idiopathic
  - Irradiation sialadenitis

*Reprinted by permission from Batsakis.[1]

TABLE 2.—*Other Causes of Parotid Enlargement**

Nutritional Factors		*Endocrine Factors*	*Drugs*	*Miscellaneous*
Malnutrition	Beriberi	Diabetes	Iodine	Allergy
Alcoholic cirrhosis	Vitamin A-deficient diet	Pregnancy and lactation	Thiouracil	Obesity
Portal cirrhosis	Celiac disease	Menopausal states	Thiocyanate	Heredity
Kwashiorkor	Bacillary dysentery	Thyroid disease	Isoproterenol	Emphysema
Cardiospasm	Chagas' disease	Stress		Idiopathic
Pellagra	Ancylostomiasis			

*Reprinted by permission from Borsanyi.[10]

in children due to chronic cheek chewing with trauma and subsequent stenosis of Stensen's duct.[8]

Parotid Enlargement in Adults

Acute suppurative parotitis in adults is marked by sudden, painful swelling of one or both glands, with fever and leukocytosis. The affecting organism is usually *S aureus* and occurs postoperatively in about a third of the cases. Predisposing factors include debilitation, dehydration and confinement to bed. This may occur in both glands in about 20 percent of cases. Diagnosis is rarely a problem and treatment consists of administering appropriate antistaphylococcal antibiotics and hydration. If the condition does not improve in 48 to 72 hours, then incision and drainage of the gland is indicated.[1-3]

Chronic suppurative parotitis presents as a recurrent, mildly painful swelling, usually associated with meals. Predisposing factors in this disease are a decreased rate of salivary flow, stasis of secretions and alteration in the character of secretions. The initial event may have been an acute infection, though other causes of decreased salivary flow such as mumps, fluid restriction, secondary cardiac disease or drug reactions have also been implicated. This decreased flow leads to stasis and inspissation of secretions resulting in ascending bacterial infection. This leads to sialectasia and chronic acinar destruction. Treatment should be conservative, with hydration and administration of sialagogues and antibiotics for acute exacerbations. If prolonged conservative measures fail, parotidectomy is the only effective surgical management.[2,3] Tympanic neurectomy has been advocated by some but most reports describe erratic results.[9]

Chronic sialectasia may represent a progressive worsening of chronic suppurative parotitis. This disorder is characterized by diffuse swelling of the parotid, progressing during a period of months to years. The postprandial swelling and pain characteristic of earlier disease may no longer be present. Histologically, this has findings similar to Sjögren's disease.[3]

Sialodochitis fibrinosis typically occurs in dehydrated patients. The history is usually of a relatively painless periodic enlargement of the gland with fluid restriction. It is caused by mucous or fibrinous plugs in the ductal system and expression of these plugs from Stensen's duct is diagnostic. Treatment consists of administering sialagogues and massage to extract the plugs.[3]

Obstruction or stricture of Stensen's duct may also lead to intermittent swelling and parotitis. This can be caused by stones or by local trauma to the duct by dentures. Management consists of ductal probing and dilation.[8]

Mycobacterium tuberculosis and atypical mycobacteria may also cause parotid enlargement either as a diffuse enlargement or a discrete mass. Cat-scratch disease and sarcoidosis are also rare causes of parotid enlargement.[2,3] These are mentioned only for completeness and will not be discussed here.

Parotitis may also occur due to administration of various drugs affecting the gland, either directly or as an idiosyncratic response.[1-3,10,11] Iodine causes a diffuse and tender swelling that may occur two to three days after injection of an iodine compound. Atropine sulfate causes enlargement of the gland by its effect on saliva, making it more viscid. Phenylbutazone produces xerostomia in about 20 percent of patients and may also give rise to a parotitis. The phenothiazine and antidepressant groups of medicines also produce xerostomia and possible parotitis on the basis of their anticholinergic effects. Isoproterenol has also been found to cause parotid enlargement, which is felt to be due to chronic sympathetic stimulation of the gland.[7-10] Different antidepressive agents were found to produce different degrees of xerostomia when tested in healthy volunteers. Salivary flow was measured after giving a single drug dose in a double-blind fashion. Administration of lithium and the monoamine oxidase inhibitors produced little change. Amitriptyline hydrochloride, imipramine hydrochloride and pamoate and nortriptyline hydrochloride caused a severe decrease in salivary flow.[11] The thiouracil class of drugs has also been noted to cause parotid enlargement. In most cases, discontinuing use of the drug will relieve the symptoms.

Metabolic Factors

Chronic asymptomatic enlargement of the parotid gland can be caused by a variety of conditions, as outlined by Borsanyi (Table 2).[10] Vitamin deficiencies are known to cause parotid enlargement, though we have seldom seen them in our patient population. Parotid enlargement is seen in 30 percent to 80 percent of patients who have alcoholic cirrhosis. Histologic features of this disorder are swelling of the acinar cells due to an increase in secretory granules, fatty infiltration and fibrosis. Sialography shows a "winter tree" appearance from displacement of ducts from each other by the fatty infiltrate. The cause of the parotitis is not

TABLE 3.—*Associated Findings in Sjögren's Syndrome*

	Sjögren's Syndrome Percent (N = 22)	*Rheumatoid Arthritis and Sjögren's Percent (N = 21)*
Recurrent parotid swelling	81	14
Lymphadenopathy	50	19
Purpura	45	4
Raynaud's phenomena	31	4
Renal	27	0
Myositis	23	0

known, but may be due to a protein deficiency. This condition is virtually nonexistent in nonalcoholic liver disease.

Diabetes mellitus has also been mentioned in association with parotid enlargement; however, the relationship is not as clear as that with cirrhosis. Obesity may also be associated with parotid enlargement due to increased fatty deposits in the gland. The pathophysiology of the parotid enlargement in these disorders is not known.

Autoimmune Diseases

Many patients will have only parotid enlargement or xerostomia, without any history suggestive of infection or obstruction and with no history of taking drugs known to affect the salivary glands. It is in this group of patients that autoimmune disorders are considered, in the spectrum of diseases that have been variously termed Mikulicz's disease or syndrome, sicca syndrome, Sjögren's syndrome and lymphoepithelial lesion. These disorders all produce the same histopathologic change seen in the salivary gland: a lymphoreticular cell proliferation usually associated with atrophy of the acinar parenchyma.

Batsakis[1] defines the terms as follows: Lymphoepithelial lesion refers to end-stage epithelial alteration showing the characteristic lymphocytic infiltration of the salivary parenchyma. Batsakis uses this term to describe a gland that is totally or nearly replaced by chronic inflammatory infiltrate in which only islands of metaplastic ducts are identified. For less advanced lesions in this spectrum, the terms chronic punctate parotitis or chronic nonspecific sialadenitis are used. These pathologic terms refer to the same lesions described by others as the clinical syndromes of chronic sialectasia or sialodochitis fibrinosis.[1] Mikulicz's syndrome is a term used in the past to describe bilateral enlargement of the lacrimal and salivary glands caused by a variety of disorders. This term is no longer preferred by Batsakis for diagnostic purposes. Sjögren's syndrome is characterized by the triad of xerostomia, keratoconjunctivitis sicca and a connective tissue disease, usually rheumatoid arthritis. It is the second most commonly occurring autoimmune disease after rheumatoid arthritis.[12]

The term sicca syndrome may be applied when xerostomia and keratoconjunctivitis sicca occur in the absence of an associated autoimmune disease. The diagnosis can be made on the basis of two of the three features and is classified as primary Sjögren's syndrome if no systemic disease is present and secondary if a connective tissue disorder is associated. This disease affects primarily women and is usually first noted in middle age. In most patients the disease runs a rather benign course manifested primarily as exocrine gland impairment. The diminution of lacrimal gland secretion leads to destruction of the corneal and conjunctival mucosa, with the findings of punctate corneal abrasions on fluorescein staining. Parotid enlargement is seen in about 80 percent of patients.[12] Xerostomia with diminished taste, mucosal ulceration, difficulty swallowing and increased dental caries are usually the major symptoms in a patient. Exocrine gland involvement of the rest of the upper respiratory tract may lead to chronic dry cough, hoarseness and bronchitis. About a fourth of patients will have extraglandular involvement, with lymphoid infiltration in the reticuloendothelial system, kidneys, muscles and lung.[12] These lymphoid infiltrates may be benign or malignant. In a study from the National Institutes of Health of observed and expected malignancies in patients who have Sjögren's syndrome, it was observed that such patients have a relative risk of lymphoma 43 times that of the normal population.[12] The risk to patients who do or do not have associated rheumatoid arthritis was similar. In patients who have Sjögren's disease with or without parotid swelling, the group with parotid swelling showed an increased risk of 66 times compared with 12 times in those with no parotid swelling. In this same study, three cases of Waldenström's macroglobulinemia developed. As this is a very rare disease, no incidence rates were available in the general population. However, the risk in Sjögren's syndrome was felt to be much greater than in the general population.[12]

The clinical course of patients with Sjögren's syndrome and rheumatoid arthritis is different from those who have primary Sjögren's. Moutsopoulos and coworkers[12] compared the clinical course of 43 patients who had Sjögren's syndrome (21 who had rheumatoid arthritis and 22 who had Sjögren's alone) in which there was a follow-up period of at least five years. Diagnosis of rheumatoid arthritis antedated the diagnosis of Sjögren's syndrome by 2 to 40 years in 16 of the 21 patients. No difference was found in the biopsy results or laboratory studies of these patients; striking differences were found, however, in the clinical manifestations.

A recurrent parotid swelling was found more often in patients with Sjögren's syndrome alone than in those who had Sjögren's and rheumatoid arthritis (Table 3). In addition, lymphadenopathy, purpura, Raynaud's phenomenon, renal involvement and myositis occurred more often in patients who had only Sjögren's than in patients who had rheumatoid arthritis and Sjögren's. There was no difference found in the incidence of pulmonary involvement with lymphoma or Waldenström's macroglobulinemia between the two groups of patients.[12]

Laboratory data on patients with Sjögren's syndrome also show differences depending on the presence or absence of rheumatoid arthritis. Of those with primary Sjögren's syndrome, 80 percent will have an increased sedimentation rate. Anemia and leukopenia occur in less than a third. More than 75 percent of the patients will have a hyperglobulinemia and numerous autoantibodies, such as rheumatoid factor, antisalivary duct antibody, antinuclear antibody and antibodies to extractable nuclear antigen.[12] There are currently four autoantibodies known in Sjögren's syndrome[2,3]: the organ-specific antisalivary duct antibody similar to the antithyroid antibody found in Hashimoto's disease and three nonorgan specific systems. These were discovered in the early 1960s. Antisalivary duct antibody is usually an IgG; its presence is inversely correlated with the degree of lymphoid infiltration, that is, those with more extensive lymphoid infiltration do not have the antibody. It was found in 69 percent of those patients who had rheumatoid arthritis and secondary Sjögren's syndrome, but in only 25 percent of those who had primary Sjögren's or who had rheumatoid arthritis without evidence of Sjögren's syndrome. The three nonorgan specific-specific antibodies are call SS-A, SS-B and rheumatoid arthritis-associated nuclear antigen. The antibodies against these three markers are found in different percentages of patients who have primary Sjögren's, Sjögren's with rheumatoid arthritis and Sjögren's with systemic lupus erythematosus. Patients who have Sjögrens syndrome alone tend to have anti-SS-B and anti-SS-A antibodies but not antisalivary gland antibody or rheumatoid arthritis nuclear antigen. Those who have Sjögren's syndrome and lupus have anti-SS-B. Patients who have Sjögren's and rheumatoid arthritis have antisalivary gland antibody but not the anti-SS-A or anti-SS-B antibodies. Differences in the histocompatibility loci (human leukocyte antigen) have also been examined in patients who have Sjögren's syndrome and those who have Sjögren's and rheumatoid arthritis.[12] Although studies have been done in only a small number of patients, differences between the human leukocyte antigen loci found in the normal population differed from those who have Sjögren's. Again, there were differences between those who have primary Sjögren's and Sjögren's with rheumatoid arthritis. These loci are hypothesized to control the immune response that causes the lymphoid infiltration of the salivary glands.[12]

As can be seen by the overlap of the above tests, these do not yet represent the definitive diagnostic answer to Sjögren's syndrome. What, then, is a reasonable and generally available battery of tests that can be used to evaluate a case involving parotid enlargement and xerostomia? As has already been alluded to, a comprehensive history and physical examination, including drug and nutritional history, are obviously important. Laboratory studies that should be done include a complete blood count, a sedimentation rate, quantitative immunoglobulins, antinuclear antibody, anti-DNA, rheumatoid factor and a chemistry panel. Most patients who have Sjögren's will show a hyperglobulinemia, usually broad-based and primarily IgG. Anti-DNA and antinuclear antibodies have been found in 10 percent of patients. Positive findings are supportive but certainly not diagnostic of Sjögren's syndrome. Of the four specific antibodies previously discussed, the SS-A, SS-B and rheumatoid arthritis nuclear antigen can be identified by sending specimens to the Scripps Reference Laboratory, 505 South Coast Blvd, La Jolla, California. The antisalivary duct antibody test is not yet available.

Ophthalmologic examination should include Schirmer's test (for keratoconjunctivitis sicca) and also fluorescein or rose-bengal staining for corneal abrasions. A Schirmer's test finding of less than 5 mm of tearing in five minutes is considered abnormal.[13,14]

Salivary flow measurements and sialochemical analysis can also be done. Sialochemical analysis will generally show an increase of the sodium and also IgA and IgG concentrations. This test is hindered somewhat by the fact that in one series an adequate specimen of saliva could only be obtained in about 30 percent of patients who had xerostomia.[14]

By far the two most widely used methods of diagnosis of Sjögren's disease are sialography and labial biopsy of the minor salivary glands. Sialography will show varying degrees of sialectasia, which is certainly not unique to Sjögren's but when correlated with the clinical history can strengthen the clinical diagnosis. The labial biopsy of the minor salivary glands still represents the surest diagnostic test for Sjögren's syndrome. The results will be abnormal in about 70 percent of the cases in patients manifesting symptoms of Sjögren's syndrome.[1] The histologic findings are atrophy and loss of acinar tissue with distortion of the lobular architecture. Lymphoid infiltration—sometimes accompanied by germinal center formation—and ductal changes including hyperplasia of the lining cells with the development of myoepithelial islands are seen. As with the disease process itself, the biopsy results show a varying degree of lymphoid change, depending on the disease state. The epimyoepithelial island that is characteristic for the disease is rarely seen on the labial biopsy specimens.[1]

Greenspan[15] attempted to quantitate the biopsy results by grading them according to the amount of lymphocyte invasion. He graded these on the basis of foci of lymphocytic invasion per 4 sq mm, with a focus being defined as 50 or more lymphocytes, histiocytes or plasma cells in one aggregate. He then examined biopsy specimens from 75 patients and additionally 53 postmortem specimens from patients who had not had Sjögren's syndrome. He found a grade 4 on biopsy specimens (more than one focus per 4 sq mm) only in those patients who were felt to have definite Sjögren's syndrome. A variable number of foci were found correlating with the degree of clinical symptoms. On the basis of his findings, Greenspan felt a grade 4 result on the biopsy specimen was diagnostic of Sjögren's syndrome.[15]

Rarely, other disorders may give an identical appearance to Sjögren's and be found only on examination of

a biopsy specimen. Amyloidosis and hemochromatosis have been reported as causes of xerostomia, diagnosed by labial biopsy.[16,17]

Treatment

Treatment of acute suppurative parotitis is straightforward and has already been mentioned. The present treatment of Sjögren's syndrome as it affects the oral cavity is symptomatic. Hormone therapy and administration of vitamins, autonomic drugs and steroids have all been used with little success. Xerostomia has been treated symptomatically by increased fluid intake and promoting salivation by chewing gum or sucking hard candy. Taking sialagogues such as SSKI (saturated solution of potassium iodide) or a solution of citric acid may occasionally be helpful, usually in the milder cases that still respond to stimulation. In these cases, repeated stimulation for one to three months may give long-term relief.[8] An artificial saliva substitute or glycerine-containing mouthwash may also be used. Meticulous dental care is essential to diminish the tendency for dental caries to occur due to xerostomia. Steroids have been used with limited success during the exacerbation of parotid swelling.

Another mode of therapy has been proposed based on the theory that the cause of Sjögren's syndrome is a lack of synthesis of prostaglandin E_1. Horrobin and Campbell[18] base this theory on several factors: prostaglandin E_1 seems to play a role in the regulation of salivary and lacrimal secretions; prostaglandin E_1 is essential for normal function of T-lymphocytes; it is an antiinflammatory agent; vitamin C deficiency inhibits prostaglandin E_1 synthesis, and Sjögren's may occur in pyridoxine deficiency.

The aim of treatment is to raise endogenous prostaglandin E_1 production by administering essential fatty acid prostaglandin E_1 precursors, pyridoxine and vitamin C. A preliminary trial using efamol, an oil high in linoleic acid, vitamin C and pyridoxine, has been undertaken. No controlled studies using this regimen have yet been reported.

Another drug whose use has occasionally been successful is bromhexine.[6,13,19,20] This is a mucolytic agent and is a synthetic derivative of vasicine, an alkaloid from the leaves of *Adhatoda vasica*. This has been tried primarily to increase tear production but has been found in several trials to have a beneficial effect on salivation. One study showed a significant increase in tearing, as measured by Schirmer's test in about 70 percent of patients. Its effect on salivary flow has been studied by using sialochemical analysis before and after treatment. Immunoglobulin and electrolyte measurements were made, as elevated sodium, IgA and IgG levels have been found in Sjögren's syndrome.[14] One study showed a decrease in IgA and sodium values with bromhexine administration but could not find any change in salivary flow.[13,19] Other studies have shown no objective improvement in flow rate, with a subjective improvement no better than in control groups using a placebo.[20] This drug has been reported on in European medical journals but is not yet available in the United States.

To illustrate the difficulties in establishing a definitive diagnosis, two cases are presented.

Reports of Cases

CASE 1. This is a 50-year-old woman who had a three-month history of parotid swelling on both sides, described as minimally tender with initially some increase in tenderness with eating. She said she had no noticeable dryness in her mouth. Her medical history was unremarkable, with no history of significant alcohol intake, diabetes, thyroid problems or arthritis. On physical examination there was bilateral, nontender, diffuse parotid enlargement with clear saliva expressed from both Stensen's ducts. The rest of the physical examination showed no abnormalities and a Schirmer's test was normal. Laboratory studies were remarkable for the findings of a sedimentation rate of 60, a serum total protein level of 8.9 grams per dl (normal 6.0 to 7.8), with an elevated IgG fraction and a positive test for rheumatoid factor. A chest x-ray film was normal. Labial biopsy and sialography were done and the results of both were normal.

CASE 2. The patient is a 69-year-old woman who for nine months had had left facial swelling and dryness in her mouth. This began following a flulike illness. Her major symptom was that of dryness, which made it difficult to eat and had resulted in a diminution of her taste. Her medical history was entirely unremarkable. On physical examination there was thick, stringy mucus expressed from the left Stensen's duct. A Schirmer's test gave abnormal results, showing less than 5 mm of tearing in five minutes. Ophthalmologic examination showed no evidence of corneal ulcerations. Laboratory studies disclosed entirely normal values. A sialogram showed punctate sialectasia of the left parotid gland and a labial biopsy specimen showed lymphocytic infiltration and acinar atrophy.

The history and laboratory findings in case 1 suggested Sjögren's syndrome, except for normal findings on a biopsy and sialogram. The patient does not meet the diagnostic criteria for Sjögren's at present and is currently being observed for any change in her symptoms.

Case 2 was interesting in that the patient dated the onset of her symptoms to a flulike illness. The lack of eye findings or evidence of an autoimmune disorder would place her in the category of chronic sialectasia with a possible viral cause.

Summary

The parotid gland may be affected by a variety of disease processes that all similarly result in enlargement and xerostomia. The limited response of the salivary glands to a multitude of insults makes diagnosis difficult. A review of some of the more common nonneoplastic disorders of the parotid gland has been

presented, along with appropriate diagnostic and treatment modalities.

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Book Reviews

The Western Journal of Medicine *does not review all books sent by publishers, although information about new books received is printed elsewhere in the journal as space permits. Prices quoted are those given by the publishers.*

DRUGS IN LITIGATION: Damage Awards Involving Prescription and Nonprescription Drugs—Second Edition—Compiled by the Editorial Staff of the publishers of LAWYERS' MEDICAL CYCLOPEDIA: Compilation Editors—Richard M. Patterson, JD, Robert E. Robinson, JD; Contributors and Consultants: H. Newcomb Morse, JD, LLM; Charles J. Frankel, MD, LLB, and Monte G. Crumley, PharmB, JD. The Allen Smith Company, 1435 North Meridian St., Indianapolis, IN 46202, 1982. 504 pages, $35.00 (softbound).

The introduction to this book describes the purpose of the text "to fill the need of the legal and medical professions for a compilation of personal injury cases involving untoward results of prescription and non-prescription drugs." Although the book is a compilation of some of these cases, its usefulness for the most part is probably limited to those attorneys involved in this type of litigation. A physician curious about such litigation might enjoy reading the case summaries, but the number of cases collected (approximately 328) is small in relation to the total drug litigation that has taken place, and the information provided in the case summaries is often very limited.

Some explanation of the way in which the cases appear to have been collected may be of assistance in understanding the book's content. The cases cited fall into two general categories. The first is lawsuits that have resulted in published appellate opinions. After a case has been tried, one or more parties may appeal. This results in a decision by the appellate court. If the court renders a written opinion, it may order that it be published. Published opinions usually include a summary of the case and how it was decided by the lower court. The book's second apparent source of case summaries is periodicals of the American Medical Association (the *Citation*) and the Association of Trial Lawyers of America. Cases in this second category were normally settled or "tried to judgment" and then described in the aforementioned periodicals in the absence of a published appellate opinion. Because so relatively few cases result in either published appellate opinions or reports in the periodicals mentioned above, the cases collected cannot be assumed to be representative of the mass of drug litigation past or present.

Furthermore, because the authors are using secondary sources there is also reason to be concerned about the accuracy of the case summaries. I have represented physicians in many cases involving alleged adverse reactions to medications and have "tried to verdict" approximately half a dozen and settled numerous others. Only one of these cases is cited in *Drugs in Litigation*. Several important inaccuracies occur in the book's summary of the case. Nevertheless, the drug at issue in the case, many of the circumstances and the result are reported correctly.

Although the limited number of cases collected does not appear representative of all drug litigation, approximately 143 different medications are nevertheless represented in the collected lawsuits. Medications receiving the most space included oral contraceptives, poliovirus vaccine, chloramphenicol, penicillin, chloroquine, diethylstilbestrol, promazine hydrochloride and oxytocin. Other drugs that are often the subject of litigation at present received limited space. Phenylbutazone, for instance, a potentially dangerous medication with manufacturer's warnings that can easily create problems for defendant physicians, was represented briefly by only three cases.

In spite of the difficulties in producing a book with such an ambitious purpose, the cases collected have been presented and indexed with thought and intelligence. For an attorney involved in the defense of physicians, this collection is useful in two ways. First, it cites case law in appellate opinions from throughout the country which may be helpful. Second, it cites cases already tried that can be the source of information discovered regarding a medication. This is important because of the general absence of reliable information on the incidence of adverse reactions to drugs. The toxic effects of many drugs likely to result in malpractice actions are of low incidence and are identified only after a drug has been marketed and used. Such reactions are reported irregularly and inconsistently. Reporting to the Food and Drug Administration by a physician is entirely voluntary and there is no other organized effort that can possibly provide an estimate of the incidence of drug reactions during use in conditions of active practice. In the absence of such pharmacologic information, knowledge gained about adverse reactions from other lawsuits can sometimes be of assistance.

The difficulties in defending physicians in drug litigation can be considerable. One common problem is the *PDR* which plaintiff's counsel often attempts to convince the jury represents the standard of care in the community. (The introduction to *Drugs in Litigation* describes the *PDR* as "the physician's Bible for drug information"!) This problem can be compounded because some of the material in the *PDR* regarding adverse reactions and warnings is ambiguous and provides a fertile field for plaintiff's counsel to argue a meaning favorable to the plaintiff. A second problem can be the codefendant drug company that may take a position damaging to the physician in attempting to divest itself of responsibility. A third problem, referred to above, is the lack of reliable information on the incidence of toxic effects of drugs as used by physicians. In these circumstances, any assistance to the physician's counsel is gladly sought and *Drugs in Litigation* can on occasion provide such assistance.

In summary, this book is a useful resource but cannot be relied on as the final authority for a vast body of litigation involving drugs.

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GYNECOLOGIC ONCOLOGY—Fundamental Principles and Clinical Practice—Volumes 1 and 2—Edited by Malcolm Coppleson, MB, BS, MD(Syd), FRCOG, FRACOG, Head, Gynecologic Oncology Unit, King George V Memorial Hospital, Royal Prince Alfred Hospital, Sydney, Australia. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1981. 1,059 pages in 2 volumes, $187.50.

This 1,059 page two-volume set represents the monumental efforts of more than 100 cancer specialists from throughout the world. The book is divided into 15 parts. Five parts are designed to cover specific principles in general oncologic management. The remaining ten discuss the various organs within the female generative tract individually. Each part is composed of selected concise chapters contributed by individual authors on isolated aspects of organ systems.

The editor states that the book is "designed as a comprehensive, authoritative, particularly detailed, and encyclopedic treatment." He has succeeded in some of these areas but not in others. The book is comprehensive in that it devotes time to all organs in the reproductive tract; however, it spends only 56 pages on carcinoma of the endometrium, the most common

gynecologic malignant condition in developed countries. The book suffers to a severe degree from organizational defects resulting in an unevenness from section to section. It is a loose association of articles contributed on selected topics. The reader is by no means confident that specific basic points will be covered and is therefore not apt to select this book as a ready reference for gynecologic oncology. Selected contributions by European authors present opinions and clinical practices that vary widely from standard oncologic practice in this country. These sections represent fascinating reports of alternative management approaches of great interest to physicians caring for patients with gynecologic malignancies. The treatment of bulky stage 11B cervical cancer by primary intracavitary radium and surgical procedures represents a significant difference in treatment philosophy between the continents. Americans reading this book should have a knowledge of standard practice in this country to appreciate these differences and to realize that these approaches may not be conventional here.

Many of the chapters represent reports of the author's personal experience and not compilations of the knowledge at large. In view of the high quality of authorship in this book, this may not necessarily represent a shortcoming. Little emphasis is given to the great advances in chemotherapy made in gynecologic oncology over the past decade.

Little guidance is given for patient treatment within the text and this will hamper its application. This two volume set is of interest to subspecialists in gynecologic oncology. It would not be an appropriate selection as the sole oncology text for practitioners or residents in gynecology.

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PRINCIPLES OF CLINICAL ELECTROCARDIOLOGY—11th Edition—Mervin J. Goldman, MD, Clinical Professor of Medicine, University of California, San Francisco, School of Medicine. Lange Medical Publications, Drawer L, Los Altos, CA 94022, 1982. 438 pages, $15.00.

The 11th edition of *Principles of Clinical Electrocardiography* by Dr Mervyn Goldman is like previous editions, in paperback, with 437 pages (full 8 by 11½ size). The book consists of 21 chapters each of which deals with a particular electrocardiographic entity. There is an excellent chapter on the introduction to electrocardiographic principles followed by a concise and to-the-point presentation of electrophysiology of the heart. Next follows definitions of the various waves and intervals on the electrocardiogram and their norms. The fourth chapter introduces the reader to the vector approach to cardiac activation and the computation of the mean QRS vector or the mean QRS axis.

Using the vectoral approach chapter 5 deals with the normal electrocardiographic patterns of the P-waves and QRS complexes as well as the ST and T waves. Subsequent chapters deal with patterns of cardiac hypertrophy, intraventricular conduction defects, myocardial ischemia, myocardial infarction, atrial arrhythmias, atrioventricular conduction defects, ventricular arrhythmias, preexcitation syndromes, aberrancy. There is also a chapter on cardiac pacing and defibrillation followed by an introduction to spatial vectocardiography. The final chapter is on an approach to the interpretation of electrocardiograms.

Several chapters have been upgraded and new information pertaining to the differential diagnosis of transmural versus nontransmural myocardial infarction included. A section on left anterior conduction delay has been added. A section on electrical pacing has been expanded and 44 new electrocardiograms have been added.

The 1st edition of Dr Goldman's book was published in 1956 and the fact that it is in its 11th edition and has been extensively translated in many languages is a testimony to its popularity.

The book makes easy reading because of the logical sequence of presentation of topics and large and simple diagrams, and the electrocardiograms that appear on just about every other page of the book. Its strongest points are the clarity with which Dr Goldman has presented the subject. A compact list of references, including both articles and reference books, is presented in the third appendix.

I have found this book extremely helpful over 12 years of teaching housestaff and students and, to expose my bias, it is the book that I read during my years of postgraduate training. This book is not meant to be an exhaustive text on the subject and is not aimed at cardiologists. Likewise, it does not present a cookbook approach to the subject for those who may be looking for such. One apparent negative feature of the book is the number of pages. However, this results from the ample size of the sketches and electrocardiograms and the prominent print. Although the text is meant to convey concepts and principles, which it does so well, it would be advantageous to the reader if a chapter on management of individual arrhythmias were included.

This book is suitable for a spectrum of students of the subject ranging from nurses, medical students, postgraduate trainees and for the medical practitioner, for whom I enthusiastically recommend Dr Goldman's latest edition on the subject.

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PAEDIATRIC CARDIOLOGY—Volume 3—Edited by Anton E. Becker, Tom G. Losekoot, Carlo Marcelletti, and Robert H. Anderson. Churchill Livingstone Inc., 1560 Broadway, New York, NY 10036, 1981. 485 pages, $65.00.

This book is a compilation of papers from an international symposium held in Amsterdam, September 1979. It is not a textbook of pediatric cardiology but it is an outstanding review of selected topics presented by cardiologists, surgeons and pathologists who are recognized authorities in their fields. Each section covers a topic and contains one to ten "chapters." Each chapter covers various aspects of the topic. Most sections are followed by question-and-answer sections that are pertinent, at times provocative and definitely informative. Most sections are "state of the art" presentations of classification of congenital heart malformations, clinical electrophysiology, transposition of the great arteries, coronary arteries in congenital heart disease, myocardial problems, axial angiography, straddling atrioventricular valves and definitive palliative surgical treatment. The section on echocardiography is selective. It contains an excellent review of contrast echocardiography and left ventricular function.

Most sections are outstanding. The section on sequential chamber analysis is a clear concise discussion with excellent illustrations of the latest attempt at taxonomy or classification of congenital heart disease. This is a controversial subject. The authors present a strong case for the use of sequential chamber and great vessel analysis as an all-encompassing and practical method of classification. The section on coronary arteries in congenital heart disease is a superbly presented and illustrated discussion of a topic that has become of great interest to pediatric cardiologists and surgeons. The recent interest has been fostered by rapid advances made in cardiac surgical procedures such as the arterial switch for transposition of the great arteries and operations requiring right ventriculotomy.

This book is highly recommended for pediatric cardiologists as a source of the latest information on selected topics. The book should also be very useful to cardiac surgeons, cardiovascular radiologists, adult cardiologists with special interest in pediatric cardiology and other health professionals who care for children with congenital heart disease.

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In Memoriam

California Medical Association

BERBLINGER, KLAUS W., San Francisco. Died November 11, 1982, in San Francisco, aged 72. Graduate of the Universität Bern, Medizinische Facultät, Bern, Switzerland, 1936. Licensed in California in 1958. Dr Berblinger was a member of the San Francisco Medical Society.

BILLMAN, HOWARD G., Marysville. Died October 14, 1982, in Yuba City of carcinoma of the prostate, aged 73. Graduate of Hahnemann Medical College, Philadelphia, 1942. Licensed in California in 1950. Dr Billman was a member of the Yuba-Sutter-Colusa County Medical Society.

CAMPION, EDWARD, San Rafael. Died November 16, 1982, in San Rafael, aged 77. Graduate of the Creighton University School of Medicine, Omaha, 1932. Licensed in California in 1932. Dr Campion was a retired member of the Marin Medical Society.

CLARY, DAVID TEMPLE, Santa Rosa. Died December 8, 1982, in Santa Rosa of cancer, aged 69. Graduate of the Creighton University School of Medicine, Omaha, 1943. Licensed in California in 1943. Dr Clary was a member of the Sonoma County Medical Association.

COTTON, BERT H., Pasadena. Died October 13, 1982, in Pasadena. aged 71. Graduate of the University of Oklahoma School of Medicine, Oklahoma City, 1937. Licensed in California in 1946. Dr Cotton was a retired member of the Los Angeles County Medical Association.

COYLE, JAMES F., San Francisco. Died November 24, 1982, aged 59. Graduate of New York University College of Medicine, New York, 1952. Licensed in California in 1962. Dr Coyle was a member of the San Francisco Medical Society.

EMPEY, LUCAS W., Carmichael. Died November 5, 1982, in Carmichael, aged 79. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1928. Licensed in California in 1929. Dr Empey was a retired member of the Sacramento-El Dorado Medical Society.

EPSTEIN, WILLIAM A., Oakland. Died November 29, 1982, aged 91. Graduate of the University of California Medical School, Berkeley-San Francisco, 1917. Licensed in California in 1955. Dr Epstein was a retired member of the Alameda-Contra Costa Medical Association.

EVANS, PHILIP J., Berkeley. Died January 6, 1983, in Berkeley, aged 54. Graduate of the University of California Medical School, San Francisco, 1959. Licensed in California in 1960. Dr Evans was a member of the Alameda-Contra Costa Medical Association.

FARIS, GEORGE ATKINSON, JR, Sonora. Died November 3, 1982, in Sonora of complications following surgical operation, aged 62. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1952. Licensed in California in 1952. Dr Faris was a member of the Tuolumne County Medical Society.

FEILER, CLIFFORD L., Lafayette. Died October 30, 1982, aged 75. Graduate of the University of California Medical School, Berkeley-San Francisco, 1939. Licensed in California in 1939. Dr Feiler was a member of the Alameda-Contra Costa Medical Association.

FITZPATRICK, THOMAS J., San Francisco. Died December 8, 1982, in San Francisco, aged 73. Graduate of the University of Illinois College of Medicine, Chicago, 1936. Licensed in California in 1936. Dr Fitzpatrick was a member of the San Francisco Medical Society.

GIRTMAN, LOUIE F., Berkeley. Died December 6, 1982, in Berkeley, aged 61. Graduate of the Medical College of Georgia, Augusta, 1944. Licensed in California in 1947. Dr Girtman was a retired member of the Alameda-Contra Costa Medical Association.

GRAY, GERALD H., Oakland. Died October 17, 1982, in Oakland, aged 83. Graduate of Harvard Medical School, Boston, 1926. Licensed in California in 1937. Dr Gray was a retired member of the Alameda-Contra Costa Medical Association.

HERTZOG, FRANCIS C., Long Beach. Died November 6, 1982, in Long Beach, aged 87. Graduate of the University of Maryland School of Medicine, Baltimore, 1917. Licensed in California in 1924. Dr Hertzog was a retired member of the Los Angeles County Medical Association.

HOGAN, JOHN M., San Diego. Died August 30, 1982, in Monterey, aged 67. Graduate of the University of Wisconsin Medical School, Madison, 1940. Licensed in California in 1948. Dr Hogan was a member of the San Diego County Medical Society.

KANTER, JOEL M., San Francisco. Was killed November 13, 1982, in a light plane crash in the East Bay Regional Park District in Berkeley, aged 40. Graduate of the University of Illinois College of Medicine, Chicago, 1966. Licensed in California in 1967. Dr Kanter was a member of the San Francisco Medical Society.

KOWALSKI, MICHAEL J., San Francisco. Died November 14, 1982, aged 82. Graduate of Stefan Batory University. Wilno, Poland, 1933. Licensed in California in 1952. Dr Kowalski was a member of the San Francisco Medical Society.

KRAUSE, MAX E., Oakland. Died September 30, 1982, aged 68. Graduate of the University of Oklahoma School of Medicine, Oklahoma City, 1939. Licensed in California in 1940. Dr Krause was a member of the Alameda-Contra Costa Medical Association.

KRUEGER, ALBERT P., Berkeley. Died December 8, 1982, aged 80. Graduate of the Stanford University School of Medicine, Palo Alto-San Francisco, 1928. Licensed in California in 1929. Dr Krueger was a retired member of the Alameda-Contra Costa Medical Association.

LEGRIS, SAMUEL F., Bakersfield. Died October 16, 1982, in San Antonio, aged 58. Graduate of Queen's University Medical School, Kingston, Canada, 1950. Licensed in California in 1955. Dr Legris was a member of the Medical Society of Santa Barbara County.

LEWIS, REUBEN R., Beverly Hills. Died November 18, 1982, aged 71. Graduate of McGill University Faculty of Medicine, Montreal, 1937. Licensed in California in 1947. Dr Lewis was a member of the Los Angeles County Medical Association.

MENSOR, MERRILL C., Daly City. Died December 18, 1982, in Menlo Park, aged 84. Graduate of the University of California Medical School, Berkeley-San Francisco, 1923. Licensed in California in 1923. Dr Mensor was a retired member of the San Francisco Medical Society.

MIZEL, MEYER L., San Francisco. Died December 3, 1982, in San Francisco, aged 77. Graduate of the University of California Medical School, Berkeley-San Francisco, 1931. Licensed in California in 1931. Dr Mizel was a member of the San Francisco Medical Society.

MORSE, DOROTHY L., San Francisco. Died October 9, 1982, in San Francisco, aged 79. Graduate of the University of California Medical School, Berkeley-San Francisco, 1928. Licensed in California in 1928. Dr Morse was a retired member of the San Francisco Medical Society.

MORTENSEN, JOHN WILLIAM, Upland. Died August 26, 1982, in Upland of cerebral degeneration, aged 55. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1953. Licensed in California in 1954. Dr Mortensen was a member of the San Bernardino County Medical Society.

NAGY, JOSEPH N., Banning. Died November 30, 1982, of injuries received in automobile accident during a heavy rain and windstorm, aged 71. Graduate of the Royal University of Ferdinand Faculty of Medicine, Regele, Rumania, 1935. Licensed in California in 1953. Dr Nagy was a member of the Riverside County Medical Association.

NEUSTADTER, RUDOLF, Walnut Creek. Died October 22, 1982, aged 86. Graduate of Friedrich-Wilhelms-Universität Medizinische Fakultät, Berlin, 1922. Licensed in California in 1939. Dr Neustadter was a retired member of the Alameda-Contra Costa Medical Association.

OSGOOD, LYLE E., Visalia. Died October 31, 1982, in San Luis Obispo, aged 70. Graduate of the University of Southern California School of Medicine, Los Angeles, 1946. Licensed in California in 1947. Dr Osgood was a retired member of the San Luis Obispo County Medical Society.

PALMER, RICHARD J., San Francisco. Died December 18, 1982, in San Francisco, aged 64. Graduate of Harvard Medical School, Boston, 1943. Licensed in California in 1950. Dr Palmer was a member of the San Francisco Medical Society.

QUINN, WILLIAM J., Alturas. Died October 26, 1982, aged 69. Graduate of Washington University School of Medicine, St. Louis, 1937. Licensed in California in 1937. Dr Quinn was a retired member of the Lassen-Plumas-Modoc-Sierra County Medical Society.

THOMAS, JOSEPH WELDON, Point Loma. Died November 24, 1982, aged 74. Graduate of Georgetown University School of Medicine, Washington, DC, 1936. Licensed in California in 1938. Dr Thomas was a member of the San Diego County Medical Society.

THORNWALL, CARLETON, Burlingame. Died December 2, 1982, in Central America, aged 49. Graduate of the State University of Iowa College of Medicine, Iowa City, 1962. Licensed in California in 1963. Dr Thornwall was a member of the San Mateo County Medical Society.

TITUS, K. WOLFGANG, Salinas. Died October 31, 1982, in Carmel, aged 59. Graduate of Northwestern University Medical School, Chicago, 1958. Licensed in California in 1958. Dr Titus was a member of the Monterey County Medical Society.

VOLLAN, DOUGLAS D., Berkeley. Died November 18, 1982, aged 61. Graduate of the University of Illinois College of Medicine, Chicago, 1943. Licensed in California in 1950. Dr Vollan was a member of the Alameda-Contra Costa Medical Association.

WILLIAMS, OWEN L., Walnut Creek. Died September 19, 1982, aged 76. Graduate of the University of California Medical School, Berkeley-San Francisco, 1942. Licensed in California in 1942. Dr Williams was a member of the Alameda-Contra Costa Medical Association.

ZEITLIN, ARTHUR PETER, Palos Verdes Estates. Died November 30, 1982, in Wilmington of myocardial infarction, aged 40. Graduate of State University of New York at Buffalo, School of Medicine, 1970. Licensed in California in 1971. Dr Zeitlin was a member of the Los Angeles County Medical Association.

Washington State Medical Association

GREENE, PHILIP B., Spokane. Died December 9, 1982, in Spokane, aged 77. Graduate of Northwestern University Medical School, Chicago, 1930. Licensed in Washington in 1931. Dr Greene was a retired member of the Spokane County Medical Society.

HARDY, JOHN L., Colfax. Died December 1, 1982, in Colfax of cancer, aged 68. Graduate of the University of Oregon Medical School, Portland, 1939. Licensed in Washington in 1940. Dr Hardy was a retired member of the Whitman County Society.

JOHNSON, DELBERT F., Seattle. Died October 31, 1982, in Seattle, aged 75. Graduate of the College of Osteopathic Medicine and Surgery, Des Moines, Iowa, 1935. Licensed in Washington in 1941. Dr Johnson was a retired member of the King County Medical Society.

SNOW, WAYNE M., Seattle. Died October 31, 1982, in Seattle, aged 59. Graduate of Temple University School of Medicine, Philadelphia, 1946. Licensed in Washington in 1949. Dr Snow was a member of the King County Medical Society.

STONE, CALEB S., JR., Seattle. Died December 1, 1982, in Seattle, aged 82. Graduate of the Washington University School of Medicine, St. Louis, 1926. Licensed in Washington in 1939. Dr Stone was a retired member of the King County Medical Society.

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Welcome: Gordon L. Nitz, M.D., NSMA President
Program Chairman: George T. Manilla, M.D.

9:00 a.m.	—	**ROBERT BOWMAN, M.D.,** Medical Director of St. Paul American Red Cross "BLOOD SUBSTITUTES—ARTIFICIAL BLOOD"
10:00 a.m.	—	**W. J. KOLFF, M.D.,** Director of Institute for Biomedical Research, University of Utah—Salt Lake City "ARE YOU UP-TO-DATE ON ARTIFICIAL ORGANS? HEART, KIDNEY & EAR"
11:00 a.m.	—	**HARMON J. EYRE, M.D.,** Division of Hematology/Oncology, University of Utah—Salt Lake City "FUTURE CLINICAL APPLICATION OF RESEARCH TOOLS IN DIAGNOSIS AND TREATMENT OF CANCER"
Noon	—	Luncheon Guest Speaker: **RICHARD MATERN, M.D.** "REFLECTIONS: PRIORITIES ON MEDICAL CARE IN NAPAL AND VIETNAM"
1:30 p.m.	—	**BOB BAR, M.D.,** Division of Endocrinology, University of Iowa "RECEPTOR SITE FUNCTION IN HUMAN DISEASE"
2:30 p.m.	—	**IRVING J. LERNER, M.D.,** Medical Oncologist, St. Paul, Minnesota—American Cancer Society "THE OLD AND NEW OF CANCER QUACKERY—A FRIDAY THE 13TH APPROACH TO TREATMENT"
3:30 p.m.	—	**JOHN L. SMITH, M.D.,** Scripps Clinic & Research Foundation "IMAGING BY NUCLEAR MAGNETIC RESONANCE"

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Invasive *Salmonella dublin* Infections Associated With Drinking Raw Milk

JOSHUA FIERER, MD, *San Diego*

Salmonella dublin *is a serotype of* Salmonella *that is host-adapted to cattle and rarely infects people. In one year (1980-1981) we diagnosed five cases of salmonellosis due to* S dublin *at the Veterans Administration Medical Center, San Diego. Four patients had positive blood cultures and one died. A sixth patient, diagnosed in 1978, had a mycotic aortic aneurysm but survived. Compared with nine patients who had* Salmonella *infections due to other serotypes, the* S dublin *patients were older, had a greater number of underlying chronic illnesses and were more seriously ill with their infections. Four of the six* S dublin *cases occurred in association with drinking "certified" raw milk from a commercial dairy.*

Two microbiologic features of S dublin *strains circulating in San Diego were distinctive. They failed to ferment arabinose and could not be grown in a minimal medium using citrate as the sole carbon source. Chronically ill elderly patients should be cautioned against drinking raw milk, an increasingly popular "health food."*

Few serotypes of *Salmonella enteritidis* that cause gastroenteritis are adapted to specific hosts; those that are adapted to lower animals seldom cause infections in humans.[1(p2)] The major exceptions are *Salmonella choleraesuis* and *S enteritidis,* serotype *dublin* (henceforth referred to as *S dublin* for clarity). Whereas the virulence of *S choleraesuis* is well known,[2] the virulence of *S dublin* is rarely commented on. Farmers and veterinarians, however, are well aware that *S dublin* infection of cattle is a major veterinary problem, and its virulence and potential for invading its natural host are well known.[3] There were few reports of human infections from *S dublin,* except occupationally in veterinarians,[4] until Werner and co-workers[5] called attention to the problem of *S dublin* in people who drink commercially distributed raw milk. Their report also suggested that *S dublin* is an unusually invasive serotype, which contradicted the impression from previous reports[6,7] that milk-borne *S dublin* infections are relatively benign.

We report a year's experience with *S dublin* infections at the Veterans Administration Medical Center (VAMC) in San Diego. We wish to emphasize the serious nature of these infections in elderly, chronically ill persons and to call attention to microbiologic characteristics that permit laboratory diagnosis of *S dublin* before serotyping can be completed.

Methods

From the records of the Microbiology Laboratory at the VAMC we identified all patients who had positive cultures for *Salmonella* sp from September 1980 through September 1981. These patients are the basis of this review.

Cultures of fecal specimens were done by standard methods.[8] Non-lactose-fermenting bacteria were identified using standard reagents.[9] Serogrouping and Vi antigen detection were done by slide agglutination using *Salmonella* grouping sera (BBL Microbiology Systems, Cockeysville, Md). Salmonellae were serotyped by the California State Department of Health. Antibiotic susceptibility testing was done by the method of Barry and associates.[10]

Results

There were 14 cases of *Salmonella* infection diagnosed at this hospital between September 1980 and September 1981, which is an average number for this hospital in a 12-month period. In five cases the infections were caused by *S dublin.* (A sixth case of *S dublin*

Refer to: Fierer J: Invasive *Salmonella dublin* infections associated with drinking raw milk. West J Med 1983 May; 138:665-669.

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Submitted, revised, July 12, 1982.

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ABBREVIATIONS USED IN TEXT

CFU = colony-forming units
VAMC = Veterans Administration Medical Center

infection diagnosed in 1978 is included in this report because it was so typical of this syndrome.) The other nine cases of *Salmonella* infection were due to five different serotypes of *S enteritidis; Salmonella typhimurium* was the only other serotype responsible for more than two cases.

All the *Salmonella* infections were community acquired. Twelve of the patients were men, reflecting the composition of our patient population. The median age of the patients in the *S dublin* cases was 76 (range, 56 to 97 years), whereas the other infections occurred in somewhat younger adults (median age 50; range, 22 to 78 years). Four of the six *S dublin* cases were associated with drinking raw milk. The patient in case 6 (from 1978) drank raw milk on one occasion two weeks before the onset of his illness; the other three patients drank raw milk several times. All the patients purchased raw milk from the same dairy, the principal source of raw milk in southern California. Not all the patients infected with other serotypes were questioned about raw milk consumption as most were not admitted to hospital and careful dietary histories were not taken. For comparison with the *S dublin* cases, we selected an age-matched control group of 15 patients admitted to hospital with non-*Salmonella* infections, and none had drunk raw milk in the month before admission (x^2, $P = .01$).

Some of the clinical features of the 15 cases of salmonellosis are summarized in Table 1. *S dublin* infections were more severe than were the infections caused by other *Salmonella* serotypes. Five of the six *S dublin* cases had bacteremia whereas only one patient in the other group had a positive blood culture. One of the cases of *S dublin* infection (case 5) was fatal. Two patients had evidence of endothelial infections. All but one of the patients who had *S dublin* infection had a serious preexisting chronic disease or were taking drugs that could have contributed to the severity of their infection.

The two cases of endothelial infection are presented below in more detail.

Reports of Cases

CASE 5. An 85-year-old woman with Paget's disease and asymptomatic calcific aortic stenosis was found to have chronic lymphocytic leukemia in 1979. In Sep-

TABLE 1.—*Comparision of 15 Patients Infected With* Salmonella dublin *and Other Serotypes of* Salmonella enteritidis, *1980-1981*

Case	*Age, Sex*	*Gastrointestinal Symptoms*	*Source of (+) Cultures*	*Temperature >38°C (100°F)*	*Underlying Illnesses*	*Therapy*	*Outcome*
S dublin							
1	80, ♂	Diarrhea	Feces	No	None	None	Improved
2	86, ♂	None	Blood	Yes	Splenectomy, PUD, vagotomy and pyloroplasty	Sulfamethoxazole-trimethoprim	Improved
3	56, ♂	Nausea, vomiting	Blood Feces	Yes	COPD	Sulfamethoxazole-trimethoprim	Improved
4	97, ♀	Nausea, vomiting, diarrhea	Blood Feces	No	Organic brain syndrome, PUD	Sulfamethoxazole-trimethoprim	Improved
5	85, ♀	Diarrhea	Blood Feces Urine	Yes	Chronic lymphocytic leukemia, calcific aortic stenosis, Paget's disease	Sulfamethoxazole-trimethoprim, chloramphenicol	Died
6*	73, ♂	None	Blood, aorta	Yes	Rheumatoid arthritis, diverticulitis	Ampicillin, surgical treatment	Improved
S enteritidis (all others)							
7	56, ♂	Diarrhea	Feces	Yes	Ulcerative colitis	None	Improved
8	22, ♂	Nausea, vomiting, diarrhea	Feces	No	None	None	Improved
9	33, ♂	Diarrhea	Feces	Yes	None	None	Improved
10	56, ♂	Diarrhea	Feces	Yes	None	None	Improved
11	29, ♂	Nausea, vomiting, diarrhea	Feces	Yes	None	Sulfamethoxazole-trimethoprim	Improved
12	34, ♂	Diarrhea	Feces	Yes	None	None	Improved
13	61, ♂	Diarrhea	Feces	No	Postgastrectomy diarrhea	None	Improved
14	63, ♂	Diarrhea	Feces	No	Diabetes mellitus	None	Improved
15	78, ♂	Diarrhea	Feces	Yes	Pulmonary fibrosis, PUD, antrectomy	Sulfamethoxazole-trimethoprim	Improved

PUD = peptic ulcer disease, COPD = chronic obstructive pulmonary disease

*Admitted to hospital and diagnosed in 1978. This case is included because of its typicality.

tember 1981 she was treated for the first time with cyclophosphamide and prednisone three times a day. A week later diarrhea, fever and chills developed and she had a syncopal episode. When she was brought to hospital her temperature was 37.6°C (99.6°F), pulse rate 90 and blood pressure 86/0 mm of mercury. She had no lymphadenopathy but her spleen was enlarged. There were bibasilar rales, her heart was enlarged and she had a midsystolic ejection murmur that radiated into her carotid arteries. Her hemoglobin level on admission was 7.4 grams per dl and her leukocyte count had fallen from 75,000 per μl (pretreatment) to 5,400 per μl, with 84 percent mature lymphocytes. She was treated initially with packed red cells, saline, cefazolin sodium and gentamicin sulfate. Pretreatment blood, urine and stool cultures all grew *S dublin.* The initial blood culture had more than 500 colony-forming units (CFU) per ml, determined from a pour plate of her blood. Blood cultures done 24 hours later were still positive, but there was less than 1 CFU per ml. Therapy was changed to trimethoprim and sulfamethoxazole given intravenously. A thoracentesis yielded clear fluid that had 5,600 leukocytes (98 percent lymphocytes), 2.6 grams per dl of protein and on culture grew a single colony of *S dublin.*

On the seventh hospital day the patient became unresponsive and was found to have third-degree heart block and pulmonary edema. A pacemaker was placed, which initially improved her heart failure. After a blood culture done that day again grew *S dublin,* treatment was changed to administration of chloramphenicol. A diagnosis of endocarditis was considered, but the patient and her family refused any further diagnostic studies. Despite treatment with digitalis and diuretics, progressive left ventricular failure developed and she died on the 17th hospital day. Permission to do an autopsy was refused.

Comment. This woman's immune status was compromised by both the leukemia and the therapy. She presented in shock with an overwhelming *Salmonella* bacteremia. The heavy bacteremia suggested an intravascular focus of infection[1(p60)] that later became apparent when heart block and progressive heart failure developed. *Salmonella* endocarditis is too uncommon to be certain whether combined medical and surgical therapy is always required, but it appears that, as in this case, medical therapy is often unsuccessful.[11]

CASE 6. A 73-year-old man with long-standing rheumatoid arthritis was taking prednisone, 10 mg a day, when he was admitted to hospital in Palm Springs, California, in May 1978 with fever, chills and abdominal pain. Blood cultures grew *S dublin,* but fecal and urine cultures did not. He was treated with ampicillin for 12 days and discharged afebrile. A week later a low-grade fever developed, and two weeks after that left lower quadrant abdominal pain prompted him to come to the VAMC. His spleen was just palpable and he had signs suggesting sigmoid diverticular perforation. His blood culture again grew *S dublin* but stool cultures were still negative. An abdominal sonogram showed a left lower quadrant mass and gallstones, but no aortic aneurysm was seen. An aortogram, however, showed an eccentric 3-cm abdominal aortic aneurysm below the renal arteries. At operation he was found to have a perforated colonic diverticulum with an abscess that did not contain *S dublin.* A colostomy was done and treatment with ampicillin, clindamycin and gentamicin was continued. Ten days later his aortic aneurysm was excised, and an aortofemoral graft was placed. Culture of a specimen of the aneurysm grew *S dublin.* Intravenous administration of ampicillin was continued for an additional six weeks, followed by oral administration of ampicillin. Three years later, the patient continues to take ampicillin and remains free of any signs of *Salmonella* aortitis.

TABLE 2.—*Biochemical Differentiation of* Salmonella dublin *From Other Group D* Salmonella *Species*

Test	S dublin* *(percent)*	Salmonella enteritidis† *(percent)*	Salmonella typhi† *(percent)*
Hydrogen sulfide (KIA)	+(100)‡	+(98)	w(94)
Citrate (Simmons)	−(0)	+(99)	−(0)
Ornithine decarboxylase	+(100)	+(99)	−(0)
Gas (glucose)	+(100)	+(100)	−(0)
Arabinose	−(0)	+(99)	−(0)
Rhamnose	+(100)	+(95)	−(0)
Trehalose	+(100)	+(100)	+(100)

KIA = Kligler's Iron Agar.

*Based on 14 strains found in San Diego County.
†Modified from Edwards and Ewing.[9]
‡+ = Positive reaction, w = weakly positive reaction, − = negative reaction.

Comment. This elderly man presented originally with *S dublin* bacteremia without an apparent source. The possibility of a mycotic aneurysm was not considered at that time. His second admission to hospital was prompted by diverticulitis, which was probably unrelated to the salmonellosis. Despite the diverticulitis, the search for a mycotic aneurysm was pursued vigorously because of the original presentation with *Salmonella* bacteremia in the absence of gastroenteritis.[12] An abdominal sonogram did not show the aneurysm, but an aortogram did.

The nine cases of salmonellosis due to serotypes other than *dublin* were typical examples of uncomplicated gastroenteritis in adults (Table 1). The age distribution and the number with underlying illnesses reflect our patient population. Only one patient required admission to hospital because of the infection (case 15) and he was also bacteremic. Interestingly, he had had a partial gastrectomy for a peptic ulcer and was taking corticosteroids, two factors that predispose to serious *Salmonella* infections.[13]

Bacteriology

All the strains of *S dublin* differed from typical strains of *S enteritidis* in that they failed to ferment arabinose and would not grow on Simmons' citrate media (Table 2).[9] All strains agglutinated with group D antiserum, and one gave a positive Vi reaction. The isolates from cases 1 through 5 were resistant to ampicillin, carbenicillin,

tetracycline and kanamycin. The isolate from case 6 was sensitive to these antibiotics but otherwise resembled the other five strains. Eight additional strains of *S dublin* found at other hospitals in San Diego had the same biochemical features as our six isolates.

Discussion

The principal difference between the *S dublin* infections and the other *S enteritidis* infections in this series was the severity of the former. The invasiveness of *S dublin* was manifested by a high incidence of bacteremia (5/6), metastatic infections (2/6) and death (1/6). Five patients were sick enough to require antibiotic therapy and admission to hospital. In contrast, none of the other *Salmonella* infections were complicated by bacteremia and only one patient was admitted to hospital and received an antimicrobial agent. In fact, the second group of patients fits the usual pattern of *Salmonella* gastroenteritis,[13] whereas *S dublin* infections resembled the bacteremic syndrome, which is more commonly associated with *S choleraesuis* infections.[1(p2)] Our experience thus confirms the report of Werner and associates,[5] who found that *S dublin* was more likely to cause bacteremia and metastatic infection than were other serotypes of *S enteritidis*. In their series of 113 cases of human *S dublin* infections diagnosed in California between 1971 and 1975, 50 percent had positive blood cultures, 17 percent died and many had metastatic infections. In that series there was a disproportionate number of cases in patients older than 50 years of age, and in them the case fatality rate was 43 percent, which suggests that this disease is particularly virulent in the elderly. In our series all the *S dublin* infections occurred in patients older than 50 years, which cannot be explained entirely by the age of our patient population as four out of nine of the patients with other *Salmonella* infections were younger than 50 years of age. Elderly people are probably predisposed to *S dublin* by virtue of their underlying diseases rather than by increased exposure.

In this series, three patients were taking prednisone, two were taking antacids and one had leukemia. These same conditions decrease resistance to all salmonellae,[13] including *S choleraesuis*.[2] However, both *S dublin* and *S choleraesuis* are more likely to present as sepsis or with metastatic infections than are other nontyphoid salmonellae, even in the absence of predisposing illnesses.[1(p2),2,6,14] Some strains of *S dublin* have a Vi antigen that is a virulence factor for *Salmonella typhi*,[15] but Vi antigen is unlikely to be the main virulence determinant for *S dublin* since only one of our six isolates had a Vi antigen. There is some evidence that not all strains of *S dublin* are equally pathogenic in cattle,[16] but no virulence mechanism has been identified in that host either.

When we reviewed the bacteriology of our *S dublin* strains, we found that all were citrate negative (Simmons' citrate agar) and did not ferment arabinose. We also tested eight other isolates of *S dublin* made in San Diego County in 1981 and all had those reactions. Using conventional media, *S dublin* could be recognized as group D, citrate- and arabinose-negative strains of *S enteritidis* (Table 2). This pattern was not apparent using the API-20E system (Analytab Products Inc, New York) in that the citrate and arabinose reactions were variable. Arabinose fermentation has been reported to be a variable feature of *S dublin*.[17] Most human isolates in England[16] and all of our strains were arabinose negative. All of our recently isolated strains were resistant to ampicillin, carbenicillin, kanamycin and tetracycline. The strain from 1978 was biochemically similar to the later isolates but was sensitive to all antibiotics. In Europe the prevalence of antibiotic-resistant *S dublin* has been increasing for the past decade.[18]

S dublin infections are uncommon in humans. In 1979 only 53 cases were reported in the United States (24 from California) out of 31,123 cases of salmonellosis.[19] The epidemiology of *S dublin* suggests that most cases are acquired from drinking contaminated milk.[5-7] Four out of six of our patients drank raw milk. *S dublin* is frequenty isolated from cattle but only rarely from other animals or feed. The association with raw milk therefore is not surprising. Because the five cases in 1980 through 1981 occurred sporadically during the year, the contamination of milk must be an ongoing but intermittent problem. This could be related to the biology of this infection in cattle because some cows become chronic, if not lifetime, carriers of *S dublin*. The presence of carriers in a herd increases the likelihood of animal-to-animal transmission, thereby perpetuating the problem.[20] Samples of certified raw milk are tested for coliform contamination, which should detect bovine fecal contamination. Unfortunately, this testing cannot eliminate the risk of *S dublin* since stress, including abortion, can reactivate latent *S dublin* infection, and in these circumstances *S dublin* may be excreted directly into the milk.[21] Even small numbers of *S dublin* introduced in this way could multiply in milk that was not adequately refrigerated at all times.

It is ironic that our patients, and presumably most others who drink raw milk, chose this product because they believed it to be healthier than pasteurized milk. Furthermore, they believed the raw milk was safe to drink because it was "certified" and sold with the approval of various government agencies. I will not comment on the validity of the nutritional claims that are made for raw milk but it is important to reiterate that heat treatment (pasteurization) is the only reliable way to ensure that milk is not contaminated by *Salmonella*.[22]

In view of the virulence of *S dublin* infection for elderly people with underlying chronic diseases, physicians should be aware of the risk of drinking raw milk and advise their patients accordingly. It would also seem appropriate for a warning notice to be placed on all containers of raw milk that are sold commercially.

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Influence of Nonthyroidal Illnesses on Serum Thyroid Hormone Indices in Hyperthyroidism

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Severe intercurrent nonthyroidal illnesses (diabetic ketoacidosis, myocardial infarction, fulminant hepatitis and bacterial pneumonia) in four thyrotoxic patients were associated with depression of total serum thyroxine (T_4) and triiodothyronine (T_3) values into the normal or even subnormal range. A diagnosis of hyperthyroidism was established by a combination of elevated radioactive iodine uptake, absent thyroid-stimulating hormone response to thyrotropin-releasing hormone or an elevated free T_4 by dialysis values. In the two of four cases that had a fatal outcome, there was a progressive decline in total T_4 and total T_3 values. In contrast, the two surviving patients had a progressive increase of total T_3 and total T_4 values into the hyperthyroid range as their underlying illness resolved. As has been seen with severe nonthyroidal illnesses, pronounced depression of total T_3 and total T_4 levels in hyperthyroid patients may also portend a poor prognosis.

Elevations of total serum thyroxine (T_4) and total triiodothyronine (T_3) concentrations constitute the usual biochemical criteria for a diagnosis of hyperthyroidism.[1,2] There have been a number of reports, however, describing subsets of hyperthyroid patients in whom only elevations of serum T_3 ("T_3 toxicosis") or, less frequently, serum T_4 ("T_4 toxicosis") are observed.[3-6] T_3 toxicosis appears to be a reflection of preferential T_3 secretion by a hyperstimulated thyroid gland, while T_4 toxicosis most commonly results from impairment of peripheral T_4 to T_3 conversion due either to intercurrent nonthyroidal illness or inadequate dietary caloric intake.[6-8]

Recently a combination of extreme depressions in total serum T_4 and total T_3 values has been described in euthyroid patients who have severe nonthyroidal illnesses, producing the so-called low T_3-T_4 state.[7-11] Theoretically, a similar phenomenon occurring in hyperthyroid patients might possibly produce normal or even subnormal serum total T_4 and total T_3 values as a result of coexisting severe nonthyroidal illness. In this report we document alterations of serum thyroid hormone indices in four hyperthyroid patients presenting with severe intercurrent nonthyroidal illnesses in which both total serum T_3 and total T_4 values were observed to be in normal or even subnormal ranges. The severity of the intercurrent nonthyroidal illness is underscored by the death of two of these patients.

Methods

Total serum T_3 and T_4 measurements were done in duplicate by standard double-antibody radioimmunoassay techniques.[12] The serum immunoassayable thyroid-stimulating hormone concentrations were measured by a commercial method (Abbott Laboratories, North Chicago, Ill). The T_3 uptake ratio was determined by an antibody-coated tube method (Clinical Assays, Cambridge, Mass) and expressed as the ratio to a normal serum pool. The free thyroxine and free T_3 indices were calculated as the product of total serum T_3 or total T_4 concentrations and the T_3 uptake ratio. The free T_4 values were measured by equilibrium dialysis[13] with purification of the tracer by polyacrylamide gel filtration before dialysis[14] and by resin after dialysis.[15] Serum antimicrosomal antibodies were measured by hemagglutination (Ames Company, Elkhart, Ind).

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ABBREVIATIONS USED IN TEXT

AST = aspartate aminotransferase
T_3 = triiodothyronine
T_4 = thyroxine

Reports of Cases

CASE 1. A 20-year-old woman was diagnosed as having insulin-dependent diabetes four months before admission and was placed on a regimen of daily insulin therapy. She presented because of chest pain, headache, sore throat and dysphagia, having stopped taking her insulin two days previously. On physical examination she was a thin woman who was anxious, alert and oriented. Her temperature was 38°C (100°F), blood pressure 100/60 mm of mercury and pulse 150 per minute. There was no exophthalmos or pretibial dermopathy. The thyroid gland was twice normal size and diffusely enlarged. The skin was warm and moist and a fine tremor of the hands was noted. Deep tendon reflexes were slightly hyperactive.

Laboratory studies disclosed the following values: hemoglobin, 13.6 grams per dl; leukocyte count, 15,000 per μl, with normal differential; normal electrolytes, and blood glucose, 800 mg per dl. The urine analysis showed 4+ sugar and a strongly positive acetone test. A roentgenogram of the chest showed a pneumomediastinum. A diagnosis of diabetic ketoacidosis was made and treatment with insulin and intravenously administered fluids begun. By the third hospital day the patient's acidosis had resolved. A chest x-ray film showed resolution of the pneumomediastinum, and an esophagogram and an upper gastrointestinal series gave unremarkable findings.

Despite clinical improvement, the patient continued to be anxious and had a persistent tachycardia of 120 a minute. Admitting serum thyroid test results were considered normal (Table 1); results of a thyroid radioactive iodine uptake (102 percent at 24 hours) and a thyrotropin-releasing hormone stimulation test (maximum thyroid-stimulating hormone response less than 1.0 μU per ml) suggested hyperthyroidism (Figure 1). Because the patient's condition appeared so improved compared with that at admission, antithyroid medication was withheld. Subsequently, total serum T_4 and T_3 values rose into the hyperthyroid range. A repeat thyrotropin-releasing hormone stimulation test (maximum thyroid-stimulating hormone response less than 1.0 μU per ml) and a T_4 suppression test (uptake of 60 percent at 24 hours) were done and administration of methimazole then begun. She was discharged home in stable condition receiving insulin and methimazole therapy.

CASE 2. The patient was a 48-year-old woman admitted to hospital in May 1980 with a myocardial infarction. Thyroid function tests at that time (Table 1) showed raised values and propylthiouracil therapy was begun. Further evaluation of her heart disease was planned, but the patient signed out of hospital against medical advice, refusing all further medication. In July 1980 she presented to another hospital and was admitted to rule out a recurrent myocardial infarction. Serum thyroid indices were again elevated (Table 1) but, before definitive treatment could be started, she once again left the hospital against medical advice.

Two weeks later she presented to the Los Angeles County/University of Southern California Medical Center after experiencing crushing anterior chest pain and breathlessness for two days. On physical examina-

TABLE 1.—*Serial Thyroid Function Tests in Four Women With Severe Intercurrent Nonthyroidal Illnesses*

Case	Hospital Day	Thyroxine (T_4) (μg/dl)	Free T_4 Index	Triiodothyronine (T_3) (ng/dl)	Free T_3 Index	T_3 Uptake Ratio	Free T_4† (ng/dl)	Antimicrosomal Antibody (AMA) Titer
1	1	6.1	9.1	103	153	1.49	...	...
	4	9.6	13.4	77	108	1.40	...	1:100
	16	10.4	14.2	...	...	1.36	...	...
	36	13.4	15.8	309	365	1.18	...	...
2	− 80*	14.8	19.7	184	245	1.33	...	...
	− 22	22.6	33.2	...	...	1.47	...	1:1,600
	− 13	18.7	34.0	...	...	1.82	...	...
	1	9.1	14.3	214	336	1.57	...	...
	3	8.1	13.5	68	114	1.67	...	...
	7	0.78	1.2	10	0	1.54	1.0	...
	13	0.54	...	10	...	...	0.4	...
3	1	8.6	12.9	152	228	1.50	...	1:1,600
	16	4.4	8.1	39	71	1.84	12.0	1:1,600
	22	4.6	7.3	49	78	1.60	...	...
4	−120	20.0	...	...	...	...	...	...
	1	22.1	28.1	342	434	1.27	...	...
	3	11.6	16.6	137	196	1.43	...	...
	6	15.5	21.5	199	276	1.39	11.9	1:100
	16	21.8	29.8	533	730	1.37	12.4	...
Normal Range		4.5-13.2	4.5-13.2	70-235	70-235	0.88-1.19	1.4-3.6	<1:100

*Hospital day −80 represents 80 days before admission.
†Measured by equilibrium dialysis.

tion she appeared chronically ill and cachectic and had a temperature of 37°C (99°F), a blood pressure of 100/60 mm of mercury and a pulse rate of 120 per minute. Pronounced bitemporal wasting was evident. There was questionable proptosis but no lid lag. The thyroid gland was 1½ times normal size, soft and not nodular. Rales were present in the left lung base. The pulse was regular and an S_3 gallop and grade 2/6 systolic murmur were heard at the left sternal border. The extremities were warm and moist and showed extreme generalized muscle wasting. Deep tendon reflexes were brisk bilaterally.

Laboratory tests disclosed the following values: hemoglobin, 8.7 grams per dl; leukocyte count, 6,900 per μl; serum creatine kinase, 569 units per liter (normal 25 to 200); serum lactate dehydrogenase, 2,075 units (normal 25 to 200) and serum aspartate aminotransferase (AST, formerly glutamic oxaloacetic transaminase), 885 units per ml (normal 5 to 40). A roentgenogram of the chest showed moderate cardiomegaly and a left pleural effusion. An electrocardiogram showed a normal sinus rhythm with depressed ST segments in the left precordial leads.

In light of the history of hyperthyroidism, treatment was begun on the second hospital day with propylthiouracil, iodides and dexamethasone (Figure 2). The patient had a complicated course with several cardiac arrests, episodes of hypotension and sepsis. With the finding of markedly subnormal total serum T_4 values, intravenous administration of thyroxine at a dose of 50 μg a day was begun. Despite vigorous therapeutic measures, the patient's condition continued to deteriorate and she died two weeks later.

CASE 3. A 26-year-old woman had been admitted to another hospital because of malaise, fatigue, nausea, light stools and dark urine for a month. She had a six-year history of intravenous heroin and methylphenidate hydrochloride (Ritalin) abuse and seven prior recorded episodes of hepatitis, the last occurring

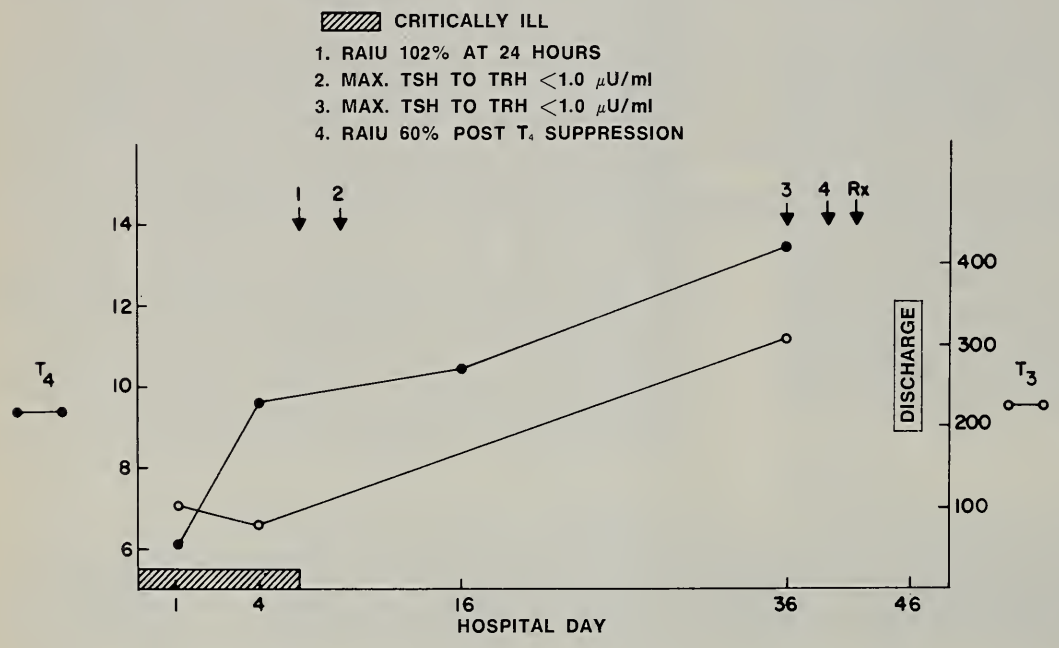

Figure 1.—Serum thyroid indices during hospital course in a 20-year-old woman with diabetic ketoacidosis. T_4 = total thyroxine, T_3 = total triiodothyronine, RAIU = radioactive iodine uptake, TSH = thyroid-stimulating hormone, TRH = thyrotropin-releasing hormone.

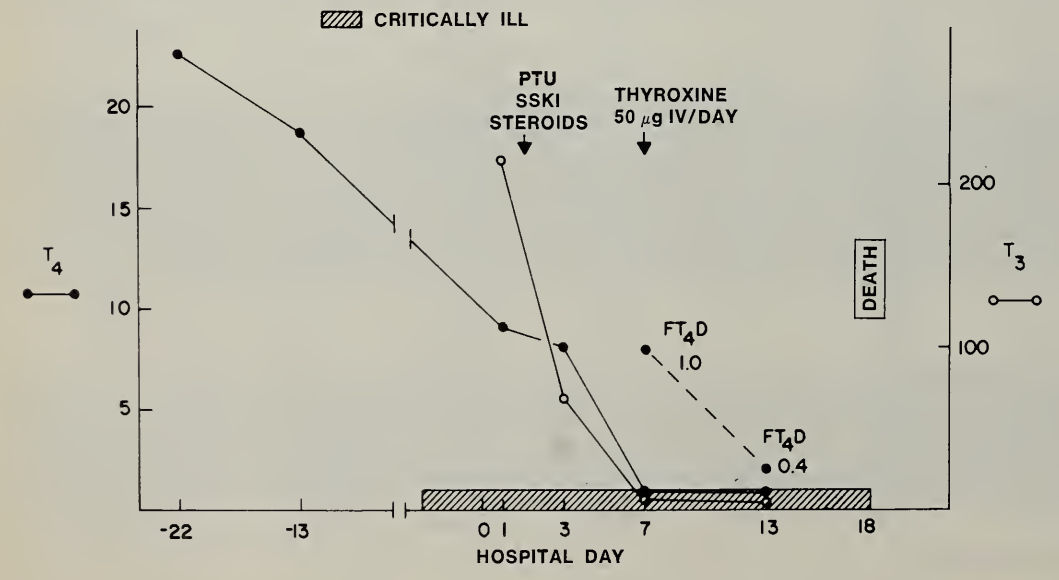

Figure 2.—Serum thyroid hormone indices in a 48-year-old woman admitted to hospital with myocardial infarction and shock. T_4 = total thyroxine, T_3 = total triiodothyronine, PTU = propylthiouracil, SSKI = saturated solution of potassium iodide, IV = intravenously, FT_4D = free T_4 measured by equilibrium dialysis (ng/dl).

six months previously. Initial laboratory studies showed a blood urea nitrogen level of 12.6 mg per dl, an AST level of 1,580 units per liter and an alanine aminotransferase (ALT, formerly glutamic pyruvic transaminase) level of 2,040 units per liter (normal, 5 to 40). A liver biopsy specimen showed features of hepatitis. Administration of prednisone, 30 mg per day, was initiated and the patient was transferred to this facility.

On physical examination on admission she appeared tremulous and acutely ill. Her temperature was 38°C (100°F), blood pressure 140/70 mm of mercury, pulse rate 140 a minute and respirations 40. Her skin was warm and deeply jaundiced. No proptosis was evident. The thyroid was three times normal size and diffusely enlarged. The lungs were clear to auscultation. The heart examination showed a tachycardia and a grade 3/6 systolic murmur. Ascites was present, along with 3+ pitting edema to both knees. Results of the initial thyroid function tests (Table 1) were within normal limits; however, the presence of a goiter led to a thyroid radioactive iodine uptake being done (55 percent at 24 hours), which indicated possible hyperthyroidism (Figure 3). Administration of propylthiouracil and propranolol hydrochloride was begun.

Despite a fall in the total serum T_4 and T_3 levels, the patient remained restless and the tachycardia persisted. A thyrotropin-releasing hormone stimulation test (maximum thyroid-stimulating hormone response less than 1.0 μU per ml) and free T_4 by equilibrium dialysis were done, the results of both confirming a hyperthyroid state. Following an increase of antithyroid medication, some symptomatic improvement was noted. The patient subsequently sustained a severe fall, however, lapsed into a coma and died shortly thereafter. The autopsy showed a 75-gram diffusely enlarged thyroid gland, which on histologic examination had features of treated Graves' disease, and a large subdural hematoma.

CASE 4. This patient is a 36-year-old woman who presented to hospital with a six-day history of fever, pleuritic chest pain, cough productive of blood-streaked sputum and increasing shortness of breath. She stated that she had an "overactive" thyroid diagnosed four months previously but that she was taking no medicines. On physical examination on admission she was

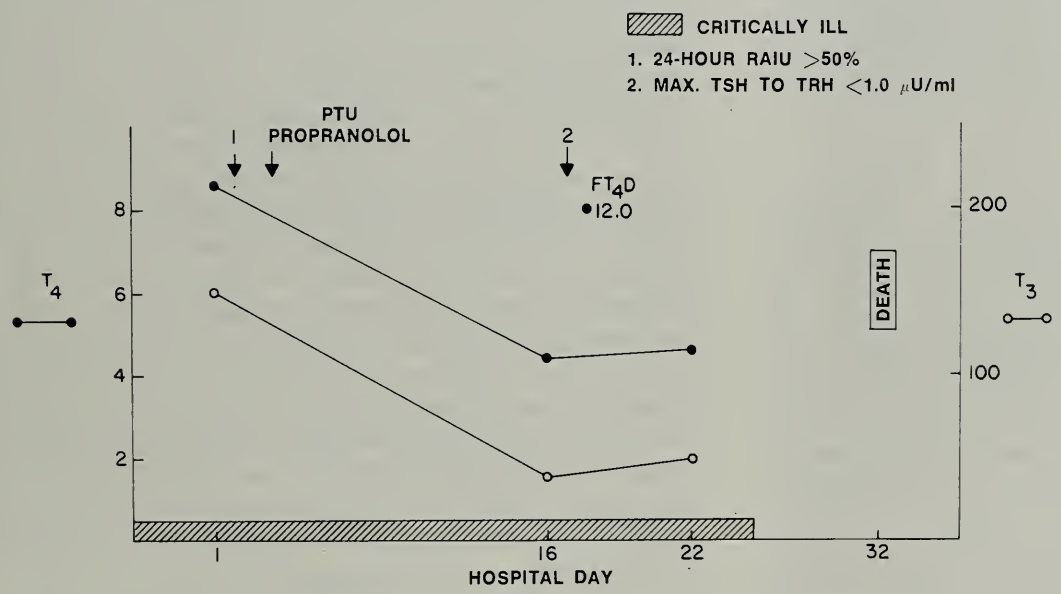

Figure 3.—Serum thyroid hormone indices in a 26-year-old woman admitted with fulminant hepatitis. T_4 = total thyroxine, T_3 = total triiodothyronine, RAIU = radioactive iodine uptake, TSH = thyroid-stimulating hormone, TRH = thyrotropin-releasing hormone, PTU = propylthiouracil, FT_4D = free T_4 measured by equilibrium dialysis (ng/dl).

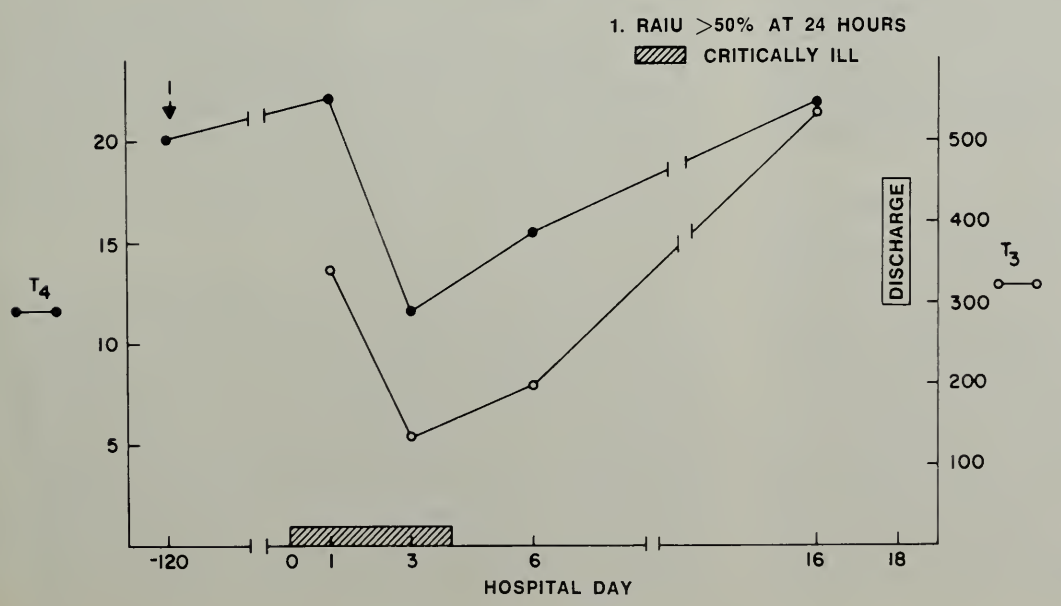

Figure 4.—Total serum thyroxine (T_4) and triiodothyronine (T_3) values in a 36-year-old woman admitted with bacterial pneumonia *(Streptococcus pneumoniae)*. RAIU = radioactive iodine uptake.

a young adult woman in severe respiratory distress. Her temperature was 40°C (104°F), pulse rate 140 a minute, blood pressure 140/80 mm of mercury and respirations 45. The skin was hot and diaphoretic. The thyroid gland was diffusely enlarged to three times normal size. Coarse rales were noted over the lower half of both lung fields. Findings on cardiac examination were unremarkable except for the tachycardia. Reflexes were normal. Laboratory test results included a hemoglobin of 13 grams per dl and the leukocyte count was 18,000 per μl with a left shift. A chest roentgenogram showed bilateral basilar infiltrates with a right pleural effusion and a significant growth of *Streptococcus pneumoniae* was cultured from a sputum specimen.

Six hours after admission the patient's temperature rose to 40.6°C (105°F) and the blood pressure fell to 70 mm of mercury systolic. She was transferred to the intensive care unit and treatment with intravenously given penicillin, dopamine and respiratory support was initiated. After 24 hours the patient's condition became stable and was greatly improved by the fourth hospital day. She continued to do well during the course of the next two weeks. Serial blood specimens showed a progressive rise in the total serum T_3 and T_4 values (Table 1, Figure 4). She was subsequently discharged on a regimen of prophylthiouracil, 100 mg orally, four times a day.

Discussion

A substantial proportion of critically ill patients who have nonthyroidal illnesses may show the "low T_3-T_4 state," as defined by depressed total serum T_3 and T_4, normal thyroid-stimulating hormone and normal or minimally elevated free T_4 by equilibrium dialysis values.[10,11] In our recently reported study of 200 patients admitted to an intensive care unit, 48 percent of the cases met these criteria for the low total T_3-total T_4 state.[16] The cause of the depression in total serum T_3 values with nonthyroidal illness is considered to be due to decreased peripheral tissue conversion of T_4 to T_3,[8] whereas the low total T_4 values may result from not fully identified circulating T_4 binding inhibitor, which interferes with the binding of T_4 to the serum carrier proteins.[17] Concomitant with clinical recovery, total serum T_4 concentrations rapidly returned to the normal range, presumably indicating removal of the putative T_4 binding inhibitor.[7]

In view of these previous studies of patients who had severe nonthyroidal illnesses, the finding in the present study of normal total serum T_3 and T_4 values in four cases of hyperthyroidism with severe illnesses should come as no surprise. In fact, inappropriately normal serum thyroid hormone concentrations in critically ill patients should raise the question of a concurrent thyrotoxic state. That we were able to accumulate four such recorded cases of "normal" serum thyroid hormone indices in the presence of hyperthyroidism indicates that this may not be an uncommon occurrence. Indeed, there are three previously reported cases of thyrotoxic patients in whom this has apparently occurred.[5,18,19] Although the reports primarily emphasized the depression of total serum T_3 values associated with nonthyroidal illnesses (that is, acute cholecystitis and diabetic ketoacidosis) despite hyperthyroidism, transient depression of total T_4 values to the normal range was also noted in these patients. However, the reduction in total T_4 values was not as prolonged, severe or as well documented as in the present study.

Two other observations deserve special comment. In case 3, one is struck by the discrepancy between the subnormal total T_4 value of 4.4 μg per dl and the greatly elevated free T_4 value by equilibrium dialysis of 12.0 ng per dl on hospital day 16. Clearly this finding would indicate a major impairment in serum thyroxine binding capacity or affinity.[7] Recently Brooks and co-workers[20] reported that patients with thyroid storm often have free T_4 values that are significantly higher than those seen in patients who have uncomplicated thyrotoxicosis. They suggested that the thyrotoxicosis, acting in concert with intercurrent systemic illnesses, might lead to a decrease in serum thyroxine binding capacity and secondarily elevations in the free fraction of T_4. This acquired defect in T_4 binding may also be analogous to the phenomenon previously discussed for patients with severe nonthyroidal illnesses.[7,11,21,22] The second point focuses on case 2 wherein serial testing showed a progressive decline in serum thyroid hormone indices as the patient's nonthyroidal illness worsened. The magnitude and the rapidity of this decline probably reflected a complex series of events that included the effect of iodide and propylthiouracil administration on suppression of thyroid hormone synthesis and releases,[2] an acquired thyroid hormone binding defect due to severe systemic illness[7] and an acceleration of peripheral T_4 clearance associated with hyperthyroidism.[23] During the terminal phase of this patient's illness, subnormal serum free T_4 values of 1.0 and 0.4 ng per dl were found. This presumably indicates that the T_4 disposal rate exceeded the production rate despite the intravenous administration of 50 μg of thyroxine daily. It is relevant to note that various medications such as glucocorticoids, heparin, salicylates and diphenylhydantoin are capable of depressing serum thyroid hormone indices by altering serum T_4 binding or metabolism.[24-27] None of the four patients in the current series, however, were receiving such drug therapy when initially displaying the depression in total T_3 and T_4 values.

The clinical assessment of hyperthyroidism in the presence of a major intercurrent systemic illness may at times be fairly subtle, requiring further laboratory studies to establish a diagnosis. In two of our cases, the diagnosis of hyperthyroidism was confirmed by the observation of an elevated radioactive iodine uptake value or the absence of a serum thyrotropin response to intravenous administration of thyrotropin-releasing hormone. Although these procedures may prove to be clinically useful, they are not entirely specific for estab-

lishing a diagnosis of hyperthyroidism. For example, an elevated radioactive iodine uptake value may be found in states of iodine deficiency, pregnancy, acquired or congenital intrathyroidal defects and in acute renal failure.[28] An absent or blunted thyroid-stimulating hormone response to thyrotropin-releasing hormone administration is also seen in elderly patients, especially men,[29] and in the presence of dopamine administration.[30] Nevertheless, if one keeps these limitations in mind, both of these procedures may be useful in documenting the diagnosis of hyperthyroidism.

An additional pitfall in the laboratory evaluation involves the accuracy of the free T_4 index (total T_4 and T_3 uptake ratio) measurement. This test produces very low free T_4 values in sick hyperthyroid patients analogous to those reported with severe nonthyroidal illnesses.[7,11,31] Although the free T_4 measurement by dialysis appears to be less affected,[7] it has the disadvantage of a long turnaround time and of being technically demanding.[13] Several commercial assays that are designed to more easily and rapidly determine the free T_4 values have been recently investigated in patients with severe nonthyroidal illnesses.[31] Some of these methods provide results comparable to free T_4 by dialysis, whereas others appear to differ grossly. Whether or not any of these commercial assays of free T_4 will prove to be accurate and reliable in all clinical settings remains to be established.

The degree of suppression of thyroid hormone indices in thyrotoxic patients who have intercurrent systemic illnesses may also indicate the ultimate prognosis.[9,10,16] It is relevant in this regard that in the two patients in this series who survived, total T_4 and T_3 values rose into the thyrotoxic range in association with clinical improvement, whereas in the two who died, total T_4 and T_3 values remained depressed or fell during the terminal phase of their illness. Clearly more extensive experience is needed to determine whether or not these alterations in thyroid indices are truly predictive in this clinical setting.

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Irradiation as an Alternative to Mastectomy for Early Breast Cancer

An Important Consideration Because of Changes in Laws

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Between May 1973 and December 1980 there were 76 patients (78 breasts) with clinical stage I or II breast carcinoma treated by biopsy and definitive radiotherapy at Stanford University Medical Center. Local-regional control has been achieved thus far in 76 of 78 cases (97 percent) with a median follow-up time of 26 months. Transient lymphedema of the breast, arm edema and breast fibrosis were the most commonly noted complications. The cosmetic result was analyzed and scored as excellent in 78 percent, satisfactory in 18 percent and unsatisfactory in 4 percent. The three unsatisfactory results occurred in patients in whom severe fibrosis developed as a result of suboptimal radiation techniques. Interdisciplinary cooperation among surgical, medical and radiation oncologists is important. The 97 percent local-regional control and the 96 percent excellent-to-satisfactory results support the use of primary radiotherapy in early stage breast carcinoma.

At the Division of Radiotherapy at Stanford University Medical Center we observed a significant change in the referral patterns of patients with cancer of the breast and we estimate that this change will be further accentuated in California by the passage in 1980 of a state bill mandating that physicians inform patients of alternative treatment methods in the management of breast cancer.* Similar legislation has been passed in Massachusetts and Minnesota.

In this paper we present a literature review of the results of primary radiotherapy in the treatment of early stage breast carcinoma and detail the Stanford University Medical Center experience with this form of treatment. Optimal care for patients with this disease requires close interaction and communication among surgical, medical and radiation oncologists. The interdisciplinary care of such patients will be emphasized, especially as it pertains to the radiotherapeutic management of this disease.

*Under California law, physicians and surgeons may be disciplined for unprofessional conduct and the law specifies what constitutes such conduct. On September 17, 1980, California Senate Bill 1893 was signed by Governor Jerry Brown, adding section 1704.5 to the state's Health and Safety Code, effective January 1981. This bill adds to the definition of unprofessional conduct the following: "the failure of a physician and surgeon to inform a patient by means of a standardized written summary . . . of alternative efficacious methods of treatment which may be medically viable, including surgical, radiological or chemotherapeutic treatments or combinations thereof, when the patient is being treated for any form of breast cancer."[1]

Review of Literature

While controversy continues regarding the use of primary radiation therapy in the management of breast carcinoma, this technique is not new. Considerable experience has been reported on from Europe where five- and ten-year results on large numbers of patients are available. In 1936 at the Fondation Curie, Francois Baclesse initiated a policy of "conservative management" that did not include mastectomy for patients who had operable breast cancer. This management has been pursued until the present, and in 1978 Calle and co-workers reported on the cases of 514 patients treated since 1960.[2] There was a minimum follow-up of five years and over half of the patients had been followed for at least ten years. In patients who had an excisional biopsy, a local control rate of 87 percent was achieved. Half of the local failures were free of disease five years following surgical salvage. Patients who had tumors greater than 3 cm had needle biopsy

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ABBREVIATIONS USED IN TEXT

CMF=cyclophosphamide, methotrexate and 5-fluorouracil
TNM=tumor-node-metastasis staging
UICC=Union Internationale Contre le Cancer

only, and in this group local relapse was high, a fact that attests to the importance of excisional biopsy.

Spitalier and colleagues from the Cancer Institute in Marseilles reported on the cases of 400 consecutive patients treated between 1960 and 1970, with a minimum follow-up of five years.[3] Treatment policy was similar to that at Fondation Curie, with excisional biopsy done only for tumors less than 3 cm. Local control was 92 percent in this group. Similarly, local control was a problem in patients who had large tumors and in whom only needle biopsy was done.

Recently Pierquin and associates[4] published the five-year results on a series of 177 patients in which they achieved local control in 93 percent of stages I and II patients. Five- and ten-year survival rates reported in this French series are comparable to results obtained in large surgical series from Memorial Sloan-Kettering (New York)[5] and Columbia Presbyterian (New York),[6] for similarly staged patients.

Peters[7] from the Princess Margaret Hospital in Toronto analyzed 217 cases of early stage breast cancer treated between 1939 and 1979 with excision and irradiation. These patients were compared with a control group treated by mastectomy and postoperative radiotherapy. The two groups were matched by age, tumor size and duration of follow-up. Local control was 93 percent in both groups. Overall survival and disease-free survival up to 30 years were not significantly different for the two groups.

Encouraged by the long-term results obtained by irradiation in Europe and Canada, Prosnitz and coworkers[8] reviewed the combined experience of four major medical centers in the United States. Local control was 93 percent in 150 stages I and II patients treated between 1962 and 1975. Since this review, there has been a rapidly growing experience at many institutions in the US. In 1979 Montague and associates[9] reported on the cases of stages I and II patients treated at MD Anderson Hospital (Houston) between 1955 and 1975. Local-regional control was 96 percent.

Hellman and colleagues[10] recently updated the experience at the Joint Center for Radiation Therapy of the Harvard Medical School (Boston) with 184 cases of stages I and II breast carcinoma. With a median follow-up of 33 months, local-regional control was 95 percent and 93 percent for stages I and II. Other medical centers in the US have reported similar results.[11-16]

Because of the long natural history of breast cancer, the US experience remains preliminary; but our two- and five-year results are in keeping with the excellent long-term results for patients treated by excisional biopsy and radiation therapy in the French series. Additionally, survival remains comparable to similarly staged patients treated with radical surgical procedure.

The Cancer Institute in Milan has recently reported the findings of a randomized trial comparing the Halsted radical mastectomy with quadrantectomy, axillary dissection and postoperative radiotherapy to the remaining breast.[17] There were 701 patients randomly selected between 1973 and 1980. Only patients who had clinical stage $T_1N_0M_0$ (tumor less than 2 cm, nodes 0, metastasis 0)* were entered. There were three local recurrences in the Halsted group and one in the quadrantectomy-radiation group. There were no differences in disease-free survival or overall survival. The authors concluded that "mastectomy appears to involve unnecessary mutilation in patients with breast cancer of less than 2 cm and no palpable axillary nodes."[17]

The National Cancer Institute has recently initiated a randomized trial to compare results of radical mastectomy with excisional biopsy and radiation. The National Surgical Adjuvant Breast Project is also conducting a randomized trial between modified radical mastectomy and segmental mastectomy, with or without postoperative radiotherapy. When the results become available, many of the questions concerning the local-regional management of early stage breast carcinoma should be answered.

During the 1970s multiple refinements in radiotherapy technique were made that improve not only local control but also the cosmetic result.[18,19] The importance of an excisional biopsy to achieve maximal local-regional control and to reduce radiation dose has been well established in both the French series and in the Harvard experience.[2,3,19] Obtaining the best cosmetic result is particularly important for a patient who finds the psychosocial impact of radical procedure unacceptable. Because breast preservation is the major advantage of primary radiotherapy, it is important to minimize posttreatment sequelae and concurrently obtain the best cosmetic result.

Because of increased public awareness concerning controversies in medical management of various diseases, particularly breast cancer, we have recently observed an increase in referrals to Stanford as patients search for treatment alternatives. We expect this trend to continue, especially in view of the recent California legislation. The current Stanford experience involving the radiotherapeutic management of breast cancer following excisional biopsy will be detailed.

Material and Methods

Patient Population

Between May 1973 and December 1980, 76 patients (78 breasts) with clinical stage I or II adenocarcinoma of the breast were treated by definitive radiotherapy at Stanford University Medical Center. All patients were

*Based on TNM staging of tumors established by the Union Internationale Contre le Cancer and the American Joint Committee for Cancer Staging and End Results Reporting (UICC/AJC).

clinically staged according to current UICC-TNM criteria.[20]

Surgical Techniques

All patients were advised to have an excisional biopsy; this was carried out in 75 of 78 lesions. Two patients had incisional biopsy and one had a needle biopsy only.

Axillary dissection was recommended to patients who were candidates for adjuvant chemotherapy and this was done in 38 patients; 11 patients had axillary samplings and 29 did not have axillary staging.

Radiation Treatment Policy

Radiation treatment techniques have been discussed previously.[11,12] Most patients received 4,500 to 5,000 rads to the breast and regional nodes. This was followed by iridium 192 (^{192}Ir) implantation to the tumor bed in 64 cases; 8 patients had electron boosts to the tumor volume, 4 had linear-accelerator boost and 2 had no additional treatment.

Follow-up and Evaluation

At each follow-up visit, in addition to routine clinical examination, multiple treatment complications were evaluated and scored as mild, moderate or severe. Breast edema, breast fibrosis, arm edema and mobility, skin discoloration and sequelae from the excisional biopsy were systematically evaluated. Breast size (A, B, C or D) was determined, with A, B and C approximating the breast cup size and D for patients who wear D cup or greater. A cosmetic result of excellent, satisfactory or unsatisfactory was given. Currently patients are being interviewed for their own evaluation of cosmesis.

TABLE 1.—*Stanford University Hospital Clinical Stages I and II Breast Cancer, May 1973 to December 1980*

Classification of Patients	Number	Tumor Stages I Number	Tumor Stages II Number
Premenopausal	44	20	24
Postmenopausal	34	12	22
TOTAL	78	32	46

TABLE 2.—*Correlation of T (Tumor) Stage With N (Node) Stage**

N Stage	T Stage T_1†	T Stage T_2‡	Total
N_0	32	30	62
N_1	9	7	16
TOTAL	41	37	78

*Staging of tumors established by the Union Internationale Contre le Cancer and the American Joint Committee for Cancer Staging and End Results Reporting (UICC/AJC).
†T_1 = tumor size less than 2 cm.
‡T_2 = tumor size more than 2 cm and less than 5 cm.

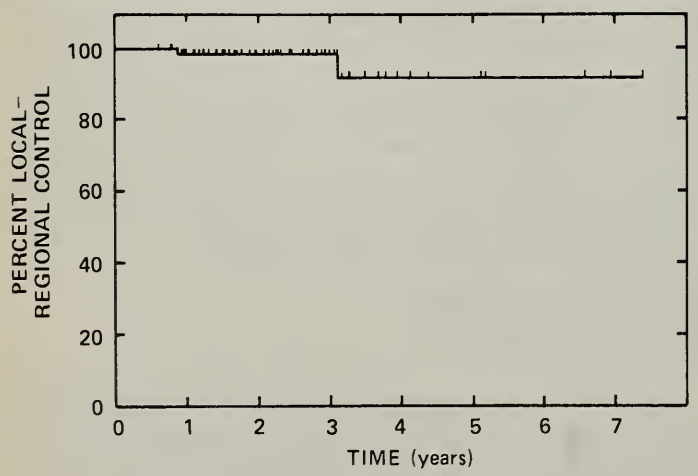

Figure 1.—Probability for local-regional control in 78 patients who have clinical stages I and II breast cancer treated by excisional biopsy and primary radiotherapy to the breast and lymph-node draining areas.

Results

Treatment Results

There were 32 cases of clinical stage I and 46 cases of clinical stage II carcinoma. In all, 44 patients were premenopausal and 34 postmenopausal (Table 1). Most patients requested referral to Stanford after refusing a mastectomy or were seeking a second opinion because of grave concerns regarding the loss of a breast. For these reasons our patients tended to be younger, with most being premenopausal (mean age, 49 years; range, 26 to 79 years).

The possibility of selection bias must always be considered in nonrandomized trials. All patients who had stages I and II cancer were considered radiation therapy candidates unless multiple masses were present in more than one breast quadrant or unless mammography showed malignant calcifications in more than one breast quadrant. There was a slight majority of T_1 tumors (Table 2); 15 of the 37 T_2 lesions were greater than 4.0 cm in size.

There have been two local-regional failures in a median follow-up time of 26 months (Figure 1). Both patients have undergone surgical salvage. One patient completed a course of cyclophosphamide, methotrexate and 5-fluorouracil (CMF) and the second patient is currently receiving CMF. They remain free of disease 10 and 15 months post relapse. Seven patients have had a systemic relapse (one stage I and six stage II). The actuarial relapse-free survival at four years is 75 percent. Six patients are alive but have disease, one patient died of disease and one patient died of a myocardial infarction 3½ years after completion of therapy. An autopsy showed no evidence of local or systemic disease.

Axillary Staging

Axillary staging was done in 38/44 (86 percent) of premenopausal patients, but only 11/34 (32 percent) of postmenopausal patients. Based on clinical-pathological findings, adjuvant chemotherapy was recommended for 12 patients and was initiated in 11 (one

refused). In all, 62 patients had a clinically negative axilla; 37 underwent axillary staging and 7 were pathologically positive, for a false-negative rate of 19 percent (7/37). Of 16 patients who had a clinically positive axilla, 12 underwent axillary staging and 4 were pathologically negative, for a false-positive rate of 33 percent (4/12). Of the four patients who had pathologically negative axillary findings, however, only two had axillary dissections; the other two patients had lower axillary lymph node biopsy only. One of the patients who had a clinically positive axilla and negative results on lower axillary lymph node biopsy subsequently had relapse in the axilla and the tail of the breast simultaneously. The other patient had a persistently positive axillary node after a low axillary biopsy. She received high-dose axillary irradiation and is free of disease.

Cosmetic Results and Complications

Analyses of cosmetic results and complications have been discussed in detail.[21] Transient lymphedema of the breast was observed following axillary dissection in 33 of 38 patients (87 percent), and actuarial analysis showed gradual improvement and resolution in two to three years. Arm edema was observed in ten patients after axillary dissection, for an incidence of 26 percent in the dissected population. Breast fibrosis was observed in 18 patients; 13 were scored mild, 2 moderate and 3 severe. The severe cases were seen following suboptimal radiation technique (high dose per fraction) used in patients treated early in the series. Transient hyperpigmentation of the skin was observed in most patients.

Uncommon complications included upper extremity thrombophlebitis in five patients, four of which immediately followed the axillary dissection. Painful post-irradiation myositis occurred in four patients. Mild radiation pneumonitis occurred in two patients, neither of whom required admission to hospital or steroid therapy. Axillary abscesses were seen in three patients, all of whom had axillary dissections.

The cosmetic result was evaluated and scored as excellent in 61 patients (78 percent), satisfactory in 14 patients (18 percent) and unsatisfactory in 3 patients (4 percent). The three poor results occurred in those in whom severe breast fibrosis developed. Eleven patients had compromised cosmesis due to a poorly planned incision at the time of excisional biopsy. This generally resulted from a vertical incision that did not run parallel to skin lines and resulted in subsequent breast retraction. Occasionally a biopsy was excessive or a single long incision was used for both the excisional biopsy and the axillary staging procedure.

There was a good correlation between the cosmetic result and the breast size. All patients with an A size had an excellent result, whereas only half of D-sized breasts were scored as excellent. However, 80 percent of patients with D breasts treated with 180 rads per fraction had an excellent result.

Discussion

Whereas breast carcinoma remains the most common cancer among women, and despite the fact that there are many large published series with varying treatments from which to draw conclusions, there continues to be heated controversy concerning the optimal management of this disease. Breast carcinoma seemingly represents a spectrum of diseases, ranging from a very aggressive, poorly responsive malignancy to a cancer with a long natural history that is responsive to multiple therapies. The many prognostic variables that have been identified, the multiple efficacious treatment modalities—both local and systemic—and the psychosocial ramifications of treatment all add to the complexity of devising a treatment plan for any one patient. This confusion has resulted in a California law that mandates that physicians are required to inform patients of "alternative efficacious methods of treatment which may be medically viable."

Both local-regional and systemic management must be considered when planning therapy. Surgical procedure, radiation therapy or combinations thereof form the basis of local therapy. Radical mastectomy has proved effective as a local treatment in early stage breast cancer,[5,6] but is associated with unacceptable morbidity for many patients, that is, loss of a breast. Because radiation therapy has been effective against other epithelial tumors, such as cancer of the cervix, prostate, and head and neck, and is beneficial in reducing local recurrence in high-risk breast cancer patients following radical surgical intervention, it should be effective in treating primary breast cancer following excisional biopsy. The large European series and evolving US experience support this contention.

The importance of removing the gross tumor by excisional biopsy for maximum local control has been well established.[2,3,19] Because the major advantage of primary radiotherapy is breast preservation, however, efforts to keep treatment sequelae to a minimum and to obtain the best cosmetic result should be made. A well-planned incision with careful attention to Langer's lines or the use of a circumareolar incision when applicable will minimize later breast retraction and deformity.[22] About 14 percent of patients in this series had a reduction in cosmesis as a result of the excisional biopsy.

In planning radiation therapy, knowledge of the precise location of the original tumor is important; that is, whether it was directly beneath the scar or somewhat adjacent, and whether the lesion was superficial or deep. This is particularly important with respect to type, location and dose of boost therapy to the tumor bed. For example, electron beam therapy to the nipple and areola frequently produces pain and discomfort and therefore centrally located lesions are best supplemented with ^{192}Ir implantation. On the other hand, in a patient with very small breasts whose tumor is located very medially on the chest wall or is overlying the pectoralis muscle, there may be insufficient breast tissue for op-

timal implantation. We have observed painful myositis in four patients in whom ^{192}Ir implants were placed in close proximity to, or inserted superficially into, the pectoralis muscles. In these patients booster therapy is best given with electrons.

The potential for early systemic spread of breast cancer is now increasingly appreciated. Adjuvant chemotherapy for breast cancer is dynamic and is evolving rapidly with increasing focus on both the timing and dose of drug administration. Patients who are candidates for adjuvant chemotherapy and for whom primary radiation is planned should have an axillary staging procedure because the state of the axillary nodes remains our best indicator of systemic disease. Either an axillary dissection or a thorough axillary sampling that resects all the nodes beneath the pectoralis muscle and inferiorly should be done. The importance of the axillary staging procedure is well known. Most series show that in 25 percent to 40 percent of patients with clinically negative axillae there will be positive nodes on axillary dissection (19 percent in this series). Additionally, some patients with clinically positive axillae may have negative dissections and can be spared full-course adjuvant chemotherapy. Of the 12 patients who were advised to have adjuvant chemotherapy in this series, 7 had a clinically negative axilla that proved to be pathologically positive, illustrating the importance of axillary dissection. Additionally, two patients who had clinically positive axillae had axillary dissections that gave negative results and thus they were advised not to receive chemotherapy. However, an additional two patients who had clinically positive axillae only had low axillary lymph node biopsy, results of which were pathologically negative, and in retrospect these two patients probably had axillary disease. We would therefore recommend a complete axillary dissection or a thorough axillary sampling in patients with clinically positive axillae in whom pathologic confirmation of disease cannot be made by frozen section at the time of axillary lymph node biopsy.

Multiple complications were associated with the axillary dissection, including lymphedema of the breast (89 percent), arm edema (26 percent), upper extremity thrombophlebitis (11 percent) and axillary abscess (8 percent). These were for the most part transient and self-limiting, however, and did not ultimately affect cosmesis.

Radiation technique was also extremely important. The most severe complications in this series, three cases of severe fibrosis, resulted from suboptimal radiotherapy technique. Thus, careful attention to the external beam therapy and appropriate selection of the type of boost therapy (^{192}Ir or electrons) are important. In conclusion, the importance of interdisciplinary cooperation in the management of patients who have early stage breast carcinoma cannot be overemphasized. Careful planning of the excisional biopsy and axillary staging, followed by careful radiotherapy technique and the appropriate timing of adjuvant chemotherapy in selected patients, are all important components of diagnosis and treatment. Primary radiation therapy has been conclusively shown to be an effective alternative to radical mastectomy in patients with T_1 lesions (with or without positive axillary nodes at dissection).[17] We must await the results of the National Cancer Institute trial and the National Surgical Adjuvant Breast Project (NSABP) cooperative trial, however, for confirmation of the efficacy of radiotherapy for larger lesions. Nonetheless, the 97 percent local-regional control and the 96 percent excellent-to-satisfactory cosmetic results achieved at Stanford support the use of primary radiotherapy as an alternative to mastectomy in the management of patients with stages I and II breast carcinoma.

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Percutaneous Renal Stone Manipulation—A Nonoperative Alternative

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Nephrostomy tube tracts, established operatively or percutaneously, can provide access to stones in the upper urinary tract. A variety of rigid or flexible urologic instruments can be used to percutaneously disintegrate or extract calculi, thus sparing a patient an operative procedure. This is most important in the case of high-risk patients, those previously operated upon or those who have active nephrolithiasis, in whom recurrent stones are prone to form. Our early experience in percutaneous renal stone disintegration and stone manipulation enabled us to remove most (in four patients) or all (again in four patients) calculi in nine patients. The procedure offers lower morbidity, shorter hospital stay and earlier return to employment than conventional operative stone procedures.

Percutaneous nephrostomy has become a widely accepted method of temporary or permanent upper urinary tract diversion associated with low morbidity. Many applications of the basic percutaneous nephrostomy have been developed and the term *endourology* has been coined to describe these closed, controlled diagnostic and therapeutic procedures.[1] Among these applications is the removal of renal and upper ureteral calculi through a nephrostomy tube tract. Rupel and Brown[2] first reported in 1941 on the endoscopic removal of an obstructing upper urinary tract calculus via an operatively placed nephrostomy tube tract. Since then several authors have described successful renal stone manipulations through already existing tube tracts placed operatively.[3-5] In 1976 Fernström and Johansson[6] first described the use of a percutaneous nephrostomy tube tract for removal of renal calculi. Herein we report our experience at the University of California, San Francisco, with percutaneous removal of renal calculi from September 1980 through January 1982.

Patients and Method

Nine patients (six women, three men, ranging in age from 34 to 69) underwent percutaneous renal stone manipulation via a nephrostomy tube tract (eight kidneys). Four tubes were placed operatively and six percutaneously (all No. 24 French). Two patients who had solitary kidneys had a mildly elevated serum creatinine level and one other patient who had bilateral renal lithiasis had an elevated serum creatinine level. Six patients had multiple calculi.

The indications for stone removal were recurrent infection (six patients), pain due to obstructing calculi (four patients) and failure to dissolve postoperatively retained stones with hemiacidrin irrigation (one). Early in our experience we chose this nonoperative approach when an operation presented a high degree of risk to a patient because of severe cardiopulmonary disease or a history of multiple renal operations. As more experience was gained, this method was offered as an elective alternative to operation for stone removal and in cases of unsuccessfully controlled metabolic stone disease in which stones were actively forming or highly likely to form in the future.

Technique

Percutaneous nephrostomy was done with the patient in the prone oblique position. Local anesthesia was used in three cases and spinal anesthesia in one case at the patient's request, though she had undergone a previous percutaneous nephrostomy (No. 8.3 French) with local anesthesia without problems. General anesthesia was done for two patients: one had the stone manipulation at the time of percutaneous nephrostomy insertion and the other was uncooperative because of mental retardation.

Under ultrasonic or fluoroscopic (or both) guidance, a 22-gauge Chiba needle is introduced through the

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posterior axillary line into the collecting system. After urine is aspirated freely, contrast material is injected for radiologic confirmation of the proper position. An 18-gauge needle of identical length is passed parallel to the original needle and, when urine flows out freely, a 0.035-inch closed-J guide wire is threaded into the collecting system and the needles are removed. The percutaneous nephrostomy tract is then carefully dilated over the guide wire with the help of commercially available (Vance) polytetrafluoroethylene dilators of No. 6 to No. 24 French. Bleeding obviously occurs during this maneuver; however, it was mild in all of our cases. In the event of severe hematuria, a nephrostomy tube of the same size as the last dilator used should be inserted to tamponade the tract. A No. 24 French Malecot or Foley catheter can be inserted over the guide wire as follows:

Malecot: A thin-walled Silastic catheter is used. A No. 14 French urethral follower with the tip removed fits smoothly into the Malecot lumen and functions as a hollow stylet (Figure 1-A). A small hole is punctured in the tip of the Malecot with an 18-gauge needle and the whole assembly is passed onto the guide wire and positioned in the renal pelvis (Figure 1-B). The "stylet"

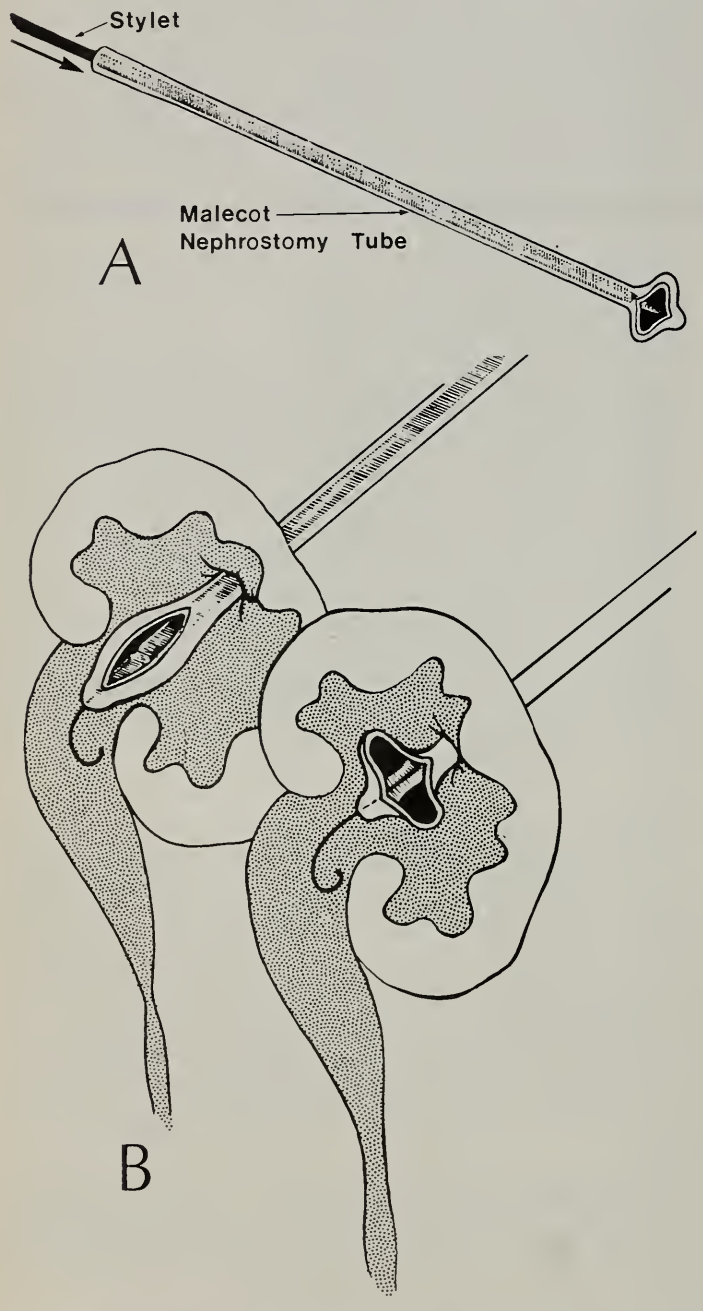

Figure 1.—Top, A No. 24 French Malecot catheter with a No. 14 French "follower stylet." **Bottom,** A Malecot catheter placed in renal pelvis; stylet withdrawn.

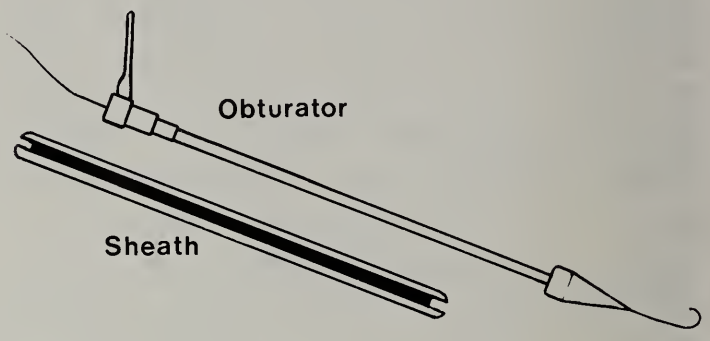

Figure 2.—A No. 26 French metal sheath with obturator and sheath that allows passage of Foley catheter balloon side arm.

Figure 3.—X-ray film of Kreutzmann nephroscopy sheath with flexible nephroscope protruding and lying adjacent to stone **(arrow).**

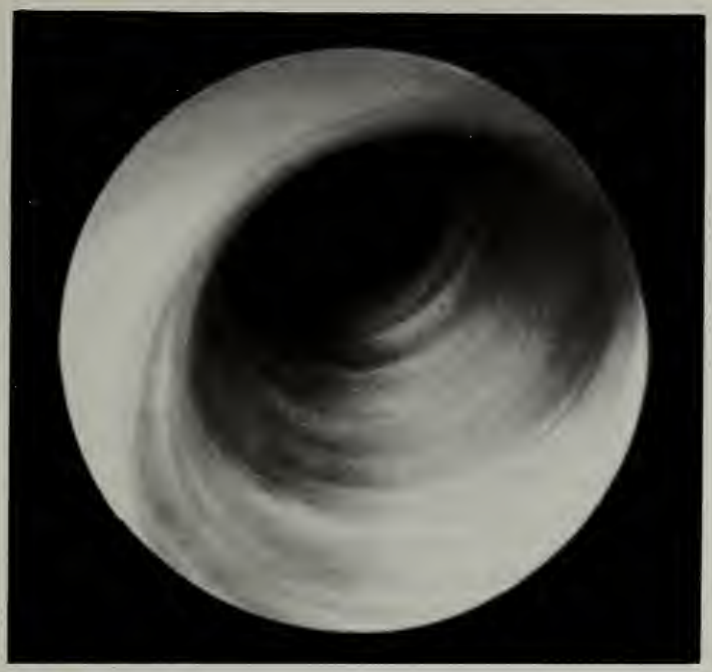

Figure 4.—Endoscopic view of nephrostomy tube tract one week after insertion.

is removed and injection of contrast medium allows radiographic confirmation of the position. The wire is then removed.[7]

Foley: A No. 26 French metal sheath with trocar is used[8] (Figure 2). The trocar obturator is hollow and can be passed over the guide wire, then removed, leaving the sheath. A No. 24 French Foley catheter fits through this sheath, and the balloon is inflated in the renal pelvis; the sheath and wire are then removed after the position has been confirmed radiographically. Alternatively, a similar sheath with a metal faceplate that is fixed to the skin can be passed over the guide wire in a similar fashion for immediate access to the collecting system. A flexible nephroscope can be used for retrieving small calculi by passing it through the fixed sheath (Figure 3).

When the procedure is completed, the patient is discharged with the nephrostomy tube left in place and is readmitted a week later for stone manipulation. During this time the tract "heals" around the tube so that when the tube is removed at the time of stone removal, the tract stays open (Figure 4) and the chosen instrument can be passed easily. Usually general or regional anesthesia is used and, in selected cases, local anesthesia.[9,10]

A wide variety of instruments is available to remove or disintegrate stones. A continuous-flow rigid nephroscope (Wolf, Rosemont, Ill; Storz, Los Angeles) that has an ultrasound lithotrite probe can be used for large stones.[11] Various baskets, forceps and graspers are used through standard cystoscopes, flexible fiberoptic nephroscopes or simply through the tract to remove smaller calculi. A nephrostomogram is done at the end of the procedure to insure that ureteral drainage is adequate.

Report of a Case

A 62-year-old woman had a history of *Proteus* urinary tract infection and bilateral renal calculi. She had had two operations on each kidney; she was currently free of stones on the left and had one large and several small right renal stones (Figure 5). At her last operation a nephrostomy tube had been left in the lower kidney pole for irrigation purposes. However, the large stone in the middle calyx was not accessible via this tract, so a percutaneous nephrostomy of the middle hydrocalyx was done (Figure 6). The large stone was disintegrated with an ultrasound lithotrite and the smaller stones were removed with a clamp passed through the tract (Figure 7).

If no postoperative irrigation is planned and the nephrostomy has been in place for a week or more, the tube does not have to be replaced. If a percutaneous nephrostomy is done with immediate stone removal, a tube should be left in place for about a week to prevent extrarenal urinary extravasation and hemorrhage.

Results

A total of ten tube tracts were used to remove various sizes and types of calculi (Figure 8). Three struvite stones, the smallest dimension of which was larger than

Figure 5.—X-ray film of kidney, ureter and bladder showing several renal calculi in a patient who has several stones in the lower pole calyces and a 2.0-cm stone in the middle calyceal group.

the diameter of the nephrostomy tube tract, were disintegrated with an ultrasonic lithotrite. One oblong stone 3.0 by 1.0 cm was manipulated longitudinally out through the tract.

Of the four patients with operatively placed nephrostomy tracts, three had residual stones (Table 1); in one the stone was entirely parenchymal, whereas the other two retained only small (1 to 4 mm) nonobstructing calculi. These two patients' calculi could not be dissolved with irrigating solutions routinely used for stone dissolution (hemiacidrin).

In the six patients who had percutaneously placed tracts, all stones but three were removed. A 2.0-cm stone was entrapped in a calyx and could not be reached with the available instruments in one patient, and two small fragments could not be manipulated after disintegration of a 2.5-cm stone in another patient. Hemiacidrin irrigation was contraindicated because of a persistently positive urine culture in both patients.

There were no life-threatening complications. All six percutaneous nephrostomy tube insertions resulted in transient mild hematuria. Seven of the nine stone manipulations resulted in the same degree of hematuria. There were essentially no changes in serum creatinine or hemoglobin values. Only one patient had an asymptomatic fall of 11 mg per dl in serum sodium level from hemodilution probably due to a high renal pelvic pressure from the irrigating fluid. In this case, the total irrigating time (noncontinuous flow system) for the manipulation was two hours. Overall average irrigating time was 1.7 hours. There were only mild edema and injection of the pelvic lining following some of the procedures. Nephrostomograms showed some intrarenal extravasation in one patient. One patient passed a 3.5-mm calculus per urethra on the first day after litholapaxy of a 2.0-cm stone.

Two of the six renal units that underwent percutaneous nephrostomy were uninfected before insertion and remained so in follow-up. Of the other four, one remains infected with an intubated cutaneous ureterostomy, whereas the other three remain uninfected on a regimen of continuous low-dose antibiotic suppression. All four renal units that had operatively placed nephrostomies were infected before manipulation. One patient, still infected, has a permanent nephrostomy. The other three are without tubes (two of them are free of infection, one is not taking antibiotics and one is receiving long-term suppressive medication). The other patient is infected and has an ileal urinary conduit.

The total hospital stay, exclusive of time for irrigation, averaged two days, which is considerably shorter

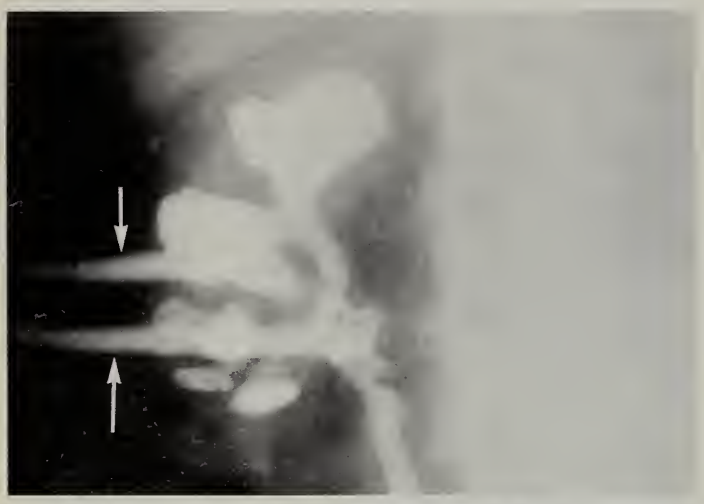

Figure 6.—A nephrostomogram of same patient as in Figure 5 showing position of two nephrostomy tubes near stones **(arrows).**

Figure 7.—Film of clamp grasping a calyceal stone directly through lower tract.

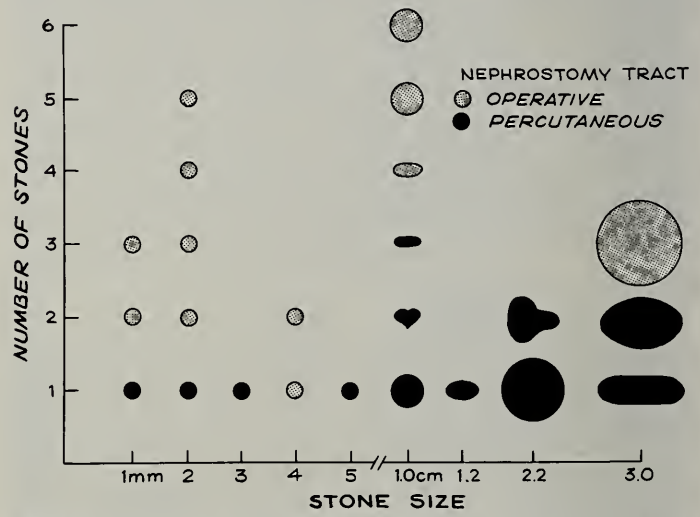

Figure 8.—Various stone sizes removed in nine patients via operatively or percutaneously placed nephrostomy tube tracts. Vertical axis represents number of stones for each size. Stones larger than 1.0 cm generally were disintegrated with ultrasonic lithotrite.

TABLE 1.—*Results of Stone Removal From Ten Nephrostomy Tube Tracts*

	Stone Free No. of Patients	*Residual Stone No. of Patients*
Operative nephrostomy tube tract	1	3
Percutaneous nephrostomy tube tract	4	2

than that necessary for an open renal operation. The two patients who were gainfully employed returned to full employment ten days (office worker) and three weeks (truck driver) after the nephrostomy tube insertion.

Discussion

Percutaneous renal stone manipulation is obviously not suitable for all patients. There are several limitations to the procedure: Stones may be inaccessible because of peculiarities of the collecting system anatomy; it is extremely difficult to puncture a nondilated system and gain access; it is not possible to do plastic repairs on an obstructed infundibulum or ureteropelvic junction, and staghorn calculi are generally too extensive for percutaneous removal and may be removed more efficiently via an open operation. Percutaneous nephrostomy, however, can be used to dissolve certain staghorn calculi.[10,12]

In this series—and in the large series from Mainz, West Germany[10]—there is minimal morbidity, preservation of renal function and improvement of infection status. Initially the primary reason to avoid an open procedure was to minimize risk in high-risk patients or to avoid a repeat renal operation, which is more difficult and subjects the renal system to additional hazard. In the series by Alken and co-workers,[10] nine patients underwent a percutaneous stone procedure because their kidneys were decompressed with a percutaneous nephrostomy when they presented with urosepsis and obstruction. Now that the procedure has proved quite successful in selected cases, it should be considered before an open intervention. It also is applicable in patients with active stone disease who are at significant risk to form stones later and consequently to be subjected to multiple procedures and, finally, in patients who refuse an open procedure.

The economic advantages of the percutaneous stone removal are evident: a shorter hospital stay and earlier return to full employment. As techniques improve, percutaneous stone removal may be done entirely on an outpatient basis. One aspect of the procedure that contributes to a shorter hospital stay and convalescence is the immediate dilatation of the tube tract to a No. 24 French. We were able to dilate to a No. 24 French at the time of the initial puncture. Gerber and associates[13] reported five cases of percutaneous nephrostomy with immediate dilatation from a No. 8 French to a No. 16 French. Alken and colleagues[10] dilated the tract immediately to a No. 10 French or a No. 16 French, then to a No. 26 French by increments during the following week. After five or six additional days the tract was ready for instrumentation.

The lower rate of stone clearance from operatively established tracts is due to several factors: They are often not straight and are more difficult to instrument; the stone is not necessarily accessible through the tract, and stones chosen for initial percutaneous nephrostomy and subsequent removal are selected for their greater chance of complete removal. Nevertheless, in a patient with an operatively placed nephrostomy who has retained or recurrent stones and in whom chemolysis is not possible or has failed, a percutaneous stone removal should be attempted.

Conclusion

Renal and upper ureteral stones can be successfully removed by using a percutaneous nephrostomy tube tract as access to the upper urinary collecting system. The procedure should be considered in patients at high risk for complications after an open procedure, those who have kidneys previously operated on, patients who have active stone disease after adequate attempts have been made to control it, patients who refuse an open surgical procedure and patients who had percutaneous nephrostomy done for urosepsis due to an obstructing stone.

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Medical Progress

The Antepartum Assessment of Fetal Well-being

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Modern obstetrics is concerned with the health and well-being of both the mother and the unborn child. During the first two thirds of this century there was a pronounced decrease in maternal mortality and morbidity related to pregnancy. More recently, using the techniques of amniocentesis, antepartum fetal heart rate testing and ultrasound, obstetricians have been able to more accurately assess the health of a fetus. This knowledge has resulted in decreased perinatal mortality and morbidity and, when rigorously applied, a decrease in fetal loss.

Sequestered in the uterus, the developing fetus has until recently been the subject of much speculation and myth. Unable to "see" or "examine" an unborn child, obstetricians considered fetal well-being to be a by-product of maternal health and welfare. A better understanding of fetal physiology and increasingly advanced technology have changed this laissez faire attitude toward the fetus. The antepartum assessment of fetal well-being is one of the primary tasks of modern obstetrical practice. The following is a brief review of the methods available to assist practitioners in the critical quest of fetal health and well-being.

The foundation for the modern obstetrical approach to the health and well-being of fetuses is the work of Sir Joseph Barcroft and his colleagues. Barcroft's book entitled *Researches on Pre-natal Life* was the first serious study of fetal physiology. Since that time other investigators have amplified and expanded our knowledge of the fetus as an entity ideally suited to survive and thrive in the intrauterine environment. Given an improved understanding of fetal physiology, an obstetrician can now ask specific questions of a fetus. Are you healthy? Are you tolerating your environment and thriving? Is it safe for you to remain where you are? Is it safe for you to be born?

Advances in obstetrical technology have provided some answers to these questions. Since 1960 three major diagnostic modalities have emerged that allow practicing obstetricians to better assess fetal health and well-being during the antepartum period. They are amniocentesis, ultrasound and continuous electronic fetal monitoring. The application of these diagnostic modalities to the assessment of fetal well-being will be discussed.

Amniocentesis

The fluid surrounding a developing fetus serves many functions. The aquatic environment allows development to proceed unencumbered by the effects of gravity and extremes of temperature fluctuation. Pulmonary and gastrointestinal function and development depend on the presence of adequate amounts of amniotic fluid. The amniotic fluid serves as a depository for various fetal by-products and wastes. From this pool an obstetrician can obtain much information about fetal well-being.

In 1953 Bevis suggested the value of amniotic fluid analysis in the assessment of hemolytic disease of the fetus.[1] Since that time amniocentesis has evolved from an in-hospital procedure to an office-based technique. Although still an integral part of the evaluation of the isoimmunized fetus, amniotic fluid analysis is useful in evaluating other fetal conditions including pulmonary maturity.

During 15 to 18 weeks of gestation, desquamated fetal cells obtained from amniotic fluid can be cultured and karyotypes developed to assess fetal chromosomes. In special circumstances, cell cultures can be used to show certain enzymatic diseases such as Hurler's syndrome (mucopolysaccharidosis type I-H). Currently a fetus can be evaluated for nearly 200 genetic or metabolic (or both) disorders in the midtrimester of pregnancy.[2] Furthermore, amniotic fluid concentration of α-fetoprotein can be determined, cor-

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related with gestational age and used as a screen for certain types of open neural tube defects. As with all invasive procedures, there are risks associated with amniocentesis in the first half of pregnancy.[3] Although exceedingly rare, fetal deaths have been reported during or immediately after amniocentesis for genetic screening. Maternal isoimmunization has also resulted from inadvertent placental puncture, leading to a feto-maternal bleed. The incidence of complications is lowest when the procedure is done by an experienced obstetrician with the aid of ultrasound. Real-time ultrasound can both locate the placenta and allow selection of a "window" for aspirating amniotic fluid. Obviously the mother/patient must be adequately informed concerning the risks and potential benefits associated with amniocentesis. A signed consent form is mandatory.

Because there are risks associated with amniocentesis for genetic screening, the following criteria have been identified to aid in the selection of patients most likely to benefit from this procedure: (1) maternal age of 35 years or older, (2) history of a chromosomal abnormality in either parent or another child, (3) parent known to be a carrier for a diagnosable metabolic disease, (4) prior delivery of a child with a neural tube defect or a parent has a neural tube defect, (5) elevated maternal serum α-fetoprotein level.

From a legal viewpoint, patients who meet any of these criteria must be *offered* genetic counseling and amniotic fluid evaluation. Failure to do so has resulted in judgments against physicians in the event of a detectable abnormality in a child at birth. A relative indication for genetic amniocentesis is excessive maternal anxiety about the possibility of a chromosomally abnormal infant. In the event adequate counseling and reassurance fail to allay her anxiety, amniocentesis may be indicated only after the risks of the procedure have been completely and fully explained.

During the second half of gestation, amniotic fluid analysis can provide insight into multiple fetal conditions, including hemolytic disease from maternal isoimmunization, fetal pulmonary maturity, fetal infection and, rarely, for evaluation of chromosomal abnormalities.

Regardless of the inciting antigen, hemolytic disease as a result of maternal isoimmunization can be a devastating problem for the fetus. Spectrophotometric evaluation of serial specimens of amniotic fluid for determination of unconjugated and total bilirubin allows an obstetrician to judge the degree of hemolysis in a fetus. Depending on the severity of the disease and fetal gestational age, treatment may be either delivery or an intrauterine fetal transfusion in an immature fetus. Most often amniotic fluid analysis identifies an affected fetus who does not need specific treatment in utero and whose delivery can be delayed until pulmonary maturity precludes a neonatal death or serious pulmonary morbidity.

Pulmonary immaturity resulting in the clinical picture of respiratory distress continues to be a leading cause of neonatal morbidity and mortality. A mature lung produces a variety of surface active agents that prevent complete alveolar collapse with each expiration. In 1971 Gluck and associates[4] described the lecithin-sphingomyelin ratio and showed its clinical usefulness in assessing functional pulmonary maturity. Other phospholipids have since been identified and incorporated into a "lung profile."[5] A mature lung profile is associated with a lecithin-sphingomyelin ratio of greater than 2:1 and a measurable amount of phosphatidylglycerol. Mature lung profiles are usually found after 35 weeks' gestation, but have been reported as early as 28 weeks in fetuses subjected to chronic intrauterine stress.

Fetal pulmonary maturity must be evaluated before any elective induction of labor or elective cesarean delivery. In cases where immediate delivery is not mandatory but is anticipated in a short time, identification of immature pulmonary state can alter obstetrical management by allowing transport of the fetus in utero to a tertiary obstetrical center. Although the lung profile offers the best assessment of pulmonary maturity, correlations between pulmonary maturity and various other amniotic fluid properties (foam stability[6] and optical density[7]) have been described. While less reliable, these tests are often simple, inexpensive and rapidly done. With a proper understanding of their limitations, they may be useful when a lung profile cannot be obtained.

In assessing patients in premature labor with or without rupture of the membranes, aspiration of amniotic fluid for microscopic examination may be useful. Whereas the presence of leukocytes in the amniotic fluid of a woman in labor is not diagnostic of an infection, the presence of bacteria is, especially if the amniotic sac is unruptured. If the sac is ruptured, the picture is less clear, but both situations call for appropriate cultures to be done, the institution of antibiotic therapy and prompt delivery. The absence of bacteria on Gram's stain or culture of the amniotic fluid is a reassuring sign that intrauterine infection is probably not the cause of the premature labor. In the absence of infection, delivery may not be indicated if the risks of prematurity are high.

Amniocentesis should also be considered in women who have unexplained hydramnios during the second half of pregnancy. Hydramnios may be the first clinical indication of congenital anomalies or chromosomal abnormalities (or both). This is especially true if the hydramnios is associated with fetal growth retardation. If careful ultrasound examination of a fetus fails to identify any gross abnormalities (such as anencephaly, gastrointestinal tract or cardiac abnormalities), the possibility of a chromosomal disorder such as trisomy 18 should be considered. Obstetrical intervention that would unnecessarily jeopardize the health of the mother may be avoided by antepartum identification of a lethal chromosomal abnormality in the fetus.[8]

Electronic Fetal Monitoring

Intermittent auscultation of fetal heart rate has long been used to evaluate fetal well-being during the ante-

partum period. However, aside from the occasional detection of a significant bradycardia (less than 100 beats per minute), tachycardia (more than 160 beats per minute) or a profound cardiac arrhythmia, simple auscultation is too sporadic, uncontrolled and imprecise to be of much use in the clinical assessment of fetal well-being.

The ability to electronically "auscultate" and record the fetal heart rate on a continuous basis has profoundly changed modern obstetrical practice. Initially, electronic monitoring of the fetal heart rate was used to assess fetal well-being during labor; in recent years, however, it has also been used to assess fetal well-being ante partum. Based on knowledge gained from observing the fetus during labor, Pose suggested that chronic intrauterine distress could be diagnosed in the antepartum period by causing uterine contractions and observing the fetal heart rate for significant changes (that is, "late" decelerations).[9] By the mid 1970s considerable experience had been acquired using the contraction stress test (also known as the oxytocin challenge test) and its usefulness in improving perinatal outcome had been clearly shown.[10] The contraction stress test serves as the standard by which all other biophysical antepartum tests are evaluated. When there is no evidence of uteroplacental insufficiency on a contraction stress test, the likelihood of a fetal loss occurring within seven days is less than 1 percent. Unfortunately false-positive results occur with a frequency approaching 50 percent. Other problems with the contraction stress test include the necessity of administering intravenous oxytocin, the inability to do the test in an office setting and that uterine contractions are contraindicated in a variety of high-risk obstetrical conditions (premature labor, placenta previa and multiple gestation).

To circumvent these problems investigators in the late 1970s proposed that fetal heart rate acceleration associated with spontaneous fetal movements, as perceived by the mother, was a sign of fetal health and correlated closely with a good perinatal outcome.[11] Druzin and co-workers[12] noted that the nonstress test might be a more sensitive indicator of fetal well-being than the contraction stress test. Although results have shown that a reactive nonstress test suggestive of a healthy fetus is rarely misleading (less than 1 percent), a nonreactive nonstress test, suggesting fetal compromise, is considerably less precise and demands further evaluation of the fetal condition. The nonstress test has generally replaced the contraction stress test as the initial antepartum screening test because of its low false-negative rate, ease of performance and lack of contraindications.[13]

Fetal movements per se have also emerged as a useful assessment of fetal well-being during the antepartum period. Sadovsky and Polishuk[14] have compared maternal perception of fetal movements with movements detected by an electromagnetic device attached to the maternal abdomen and reported an 87 percent correlation. Maternal perception of fetal movements begins at about 16 to 18 weeks' gestation, with the peak frequency of movements occurring between 29 and 38 weeks' gestation. Just before delivery there may be a perceptible diminution in fetal movements but, even during labor, fetal activity is common. While the total number of fetal movements varies widely (4 to 1,440 movements per day), each fetus usually has a recognizable movement pattern. When there is a dramatic decrease in the number of fetal movements or a loss of normal movement pattern, the chance of impending fetal demise is great.

Sadovsky and Polishuk taught 164 mothers with both normal and high-risk pregnancies to recognize the daily movement pattern of their fetuses and then followed the pregnancies prospectively. In 50 patients there was a dramatic decrease of fetal movements. Of these, 22 fetuses died in utero whereas the other 28 were delivered as soon as the change occurred. They concluded that "reduction in fetal movements from high, constant, or fluctuating levels, to less than 4 per day or the complete cessation of movement with heart sounds still audible for at least 12 hours, points to a severely distressed fetus and impending death."[14]

Comparing daily assessment of fetal movement with results of either the contraction stress test or the nonstress test, Rayburn and associates[15] found that an active fetus predicted a favorable pregnancy outcome as reliably as either of the tests. Further, an inactive fetus with an abnormal antepartum fetal heart rate was highly predictive of a poor perinatal outcome.

Antepartum assessment of fetal well-being requires constant vigilance on the part of both mother and obstetrician. Using maternal perception of daily fetal movements as a screen is a simple and inexpensive method of evaluating fetal well-being in a compliant patient. When there appears to be a significant reduction or alteration in the number or pattern of fetal movements, the nonstress test or contraction stress test should be used to further evaluate fetal well-being.

Ultrasound

Only recently have obstetricians been able to visually examine the whole fetus. Previous radiographic and static ultrasound techniques allowed visualization of fetal parts or contour at a single point in time. With the development of real-time ultrasonographic imaging, the fetus can be seen in its dynamic and lively form. It is now possible to examine a fetus for birth defects and to assess accurately fetal tone and movement, organ size and pathology and, in some cases, organ function. This ability has provided obstetricians the exciting possibility of actually treating certain fetal conditions in utero.

There are multiple indications for ultrasound examinations in obstetrical practice. Early in gestation the identification of an intrauterine sac and crown-rump length as well as the number of sacs can reliably date a pregnancy to within a week or less or detect the presence of multiple gestation. Ultrasonographic visualization of the amniotic fluid cavity and placental location can minimize the risks of genetic amniocentesis and facilitate the aspiration of amniotic fluid for genetic

studies. By viewing a growing fetus we can identify a variety of congenital abnormalities without exposing either mother or fetus to the risks of irradiation.

In addition, ultrasonography can assess fetal age with some accuracy by measuring biparietal diameter, abdominal circumference and femur length. The adequacy of incremental fetal growth can also be evaluated with ultrasound and provide a clinician an estimate of fetal weight. As fetal growth and development continue, the diagnosis of certain congenital abnormalities becomes more obvious. This advance warning provides an obstetrician valuable time to plan the mode of delivery and, if indicated, to arrange any immediate postnatal therapy. Alternatively, the diagnosis of a lethal congenital anomaly may prevent unwarranted obstetrical intervention, thus protecting maternal health. Ultrasonography can help diagnose the cause of third-trimester vaginal bleeding by accurately locating the site of placental implantation. In the intrapartum period ultrasound can be used to establish fetal presentation in singleton or twin gestation, confirm viability and estimate fetal weight.

Perhaps the greatest potential usefulness of ultrasound is in its ability to guide an obstetrician during therapeutic in utero interventions on behalf of a compromised fetus. It is now possible to do intrauterine fetal transfusions without the use of fluoroscopy.[16] Accurate placement of a transfusion needle in the fetal peritoneal cavity can be confirmed by real-time ultrasound. Recently we have described a technique of placing a ventriculoamniotic shunt in the dilated lateral ventricles of fetuses with hydrocephalus.[17] Such a technique would not be possible without the availability of real-time ultrasound guidance.

Ultrasound technology has become a vital part of the antepartum assessment of fetal well-being. It is increasingly important that practicing obstetricians gain experience in the use of real-time ultrasound equipment under expert supervision. Only in this way can the misuse or misapplication of ultrasound be prevented.

Biophysical Profile

The assessment of fetal well-being and the identification of patients at risk for fetal death are major tasks of modern obstetricians. Obstetrical technology has given practitioners the ability to "see" a fetus, to sample its environment and to continuously monitor fetal cardiac activity. Such an intensive approach to fetal assessment results in a clear reduction in fetal loss. Manning and colleagues have combined many of the fetal assessment techniques discussed above into what is termed a fetal "biophysical profile."[18] This profile represents an evaluation by ultrasound of a fetus's general movements, muscle tone, breathing movements and the adequacy of amniotic fluid, as well as the results of a nonstress test. This approach was used to assess 1,184 referred high-risk obstetrical patients. A significant reduction in perinatal mortality was achieved (5.1 per 1,000 births in the study group versus 65 per 1,000 expected in a high-risk group, or versus 14.3 per 1,000 births in the general population).

Clearly the rigorous application of modern obstetrical technologies has enabled practicing obstetricians to more accurately assess the state of a fetus in utero. This ability is essential if continued reductions in fetal mortality and morbidity rates are to be realized. The application of this knowledge is also essential if risks to maternal health and well-being are to be kept to a minimum.

Summary

Early diagnosis of fetal genetic disorders, congenital abnormalities or metabolic disturbances can in some cases lead to a reduction in the incidence of poor pregnancy outcome. Assessment of a fetus confronted by the stresses of maternal diseases, abnormal placentation or pregnancy-related conditions can allow for either expeditious delivery of the fetus or the avoidance of unnecessary obstetrical intervention. Modern obstetrical technologies enable practicing obstetricians not only to diagnose but in some cases to ameliorate or even treat certain fetal conditions and thereby improve perinatal outcome. The next few years hold the promise of even more exciting possibilities as genetic diagnosis and treatment become possible and as new techniques to evaluate and aid a pregnancy are developed. With the use of these new technologies, the art of obstetrics is committed to reducing fetal and neonatal mortality and morbidity rates to an absolute minimum. This improvement in the quality of life for newborns must be achieved without jeopardizing the safety and health of mothers.

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Specialty Conference

Preventing Infection in Neutropenic Cancer Patients

Participants

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ARNOLD S. BAYER, MD:* *Every year more than 20,000 patients in the United States die of leukemia, while an even larger number die of solid tumors. A substantial proportion of these deaths is attributable to infection (in cases of leukemia, for example, as high as 75 percent).*[1] *With the increasingly frequent use of aggressive cytoreductive chemotherapy in the treatment of solid tumors, infection threatens to become an even more frequent and serious problem. Severe systemic infections in compromised hosts are associated with an overall mortality of about 80 percent; even with early institution of empiric antimicrobial therapy, death rates of 20 percent to 50 percent are not uncommon.*[2] *Over the past decade, therefore, attention has turned to the concept of infection prevention in such immunocompromised hosts. This will be the topic of this conference.*

Many years ago it was appreciated clinically that among patients with malignancy, leukopenia was an important predisposing factor for acquiring bacterial infections (Figure 1)[3]*; moreover, this risk became particularly striking at total granulocyte counts of less than 1,000 per μl. Although there are many other variables that contribute to an increased risk of infection, for the purposes of this conference we will be discussing primarily leukopenic patients who have leukemia, solid tumors or lymphoreticular malignant conditions and who are being treated with immunosuppressive chemotherapy. We will refer to these patients descriptively as "neutropenic cancer patients." Dr Steven Beutler will discuss how these patients initially acquire their infection and what can be done to prevent this acquisition. Dr Neil Barth will then discuss the use of protective environments for neutropenic cancer patients and ways of enhancing host defenses in such patients.*

Infections in Neutropenic Patients

STEVEN M. BEUTLER, MD:† In the early 1970s Schimpff and colleagues[4] studied surveillance cultures in neutropenic cancer patients. They found that about half of such patients became infected with organisms they harbored before hospital admission, whereas the other half became infected with flora acquired after entering the hospital. Regardless of the timing of initial acquisition, virtually all neutropenic cancer patients first became "colonized" with the etiologic organisms at variable times before the onset of the infectious syndrome. Sites commonly colonized included gingiva, anterior urethra, anterior nares and axilla. The most heavily colonized areas, though, were the rectum and perineum. For example, in one study about 75 percent of the *Pseudomonas* strains that later caused infection were first isolated from the rectum on surveillance cultures. This prompted speculation that perhaps by decreasing the bacterial "burden" of the gastrointestinal tract, the frequency of infection could also be reduced. To test this hypothesis, neutropenic patients were treated with a regimen of oral nonabsorbable antibiotic agents,[5-12] with combinations of gentamicin sulfate, vancomycin hydrochloride and nystatin (GVN) being the most widely used in early studies. Because this regimen was given orally, it was hoped that it would sterilize all parts of the gastrointestinal tract, from the mouth to the anus. The antibiotics included in this regimen were active against most of the potentially pathogenic flora that inhabit the gastrointestinal tract (for example, gentamicin against aerobic Gram-negative bacilli; vancomy-

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ABBREVIATION USED IN TEXT

TMP-SMX=trimethoprim-sulfamethoxazole

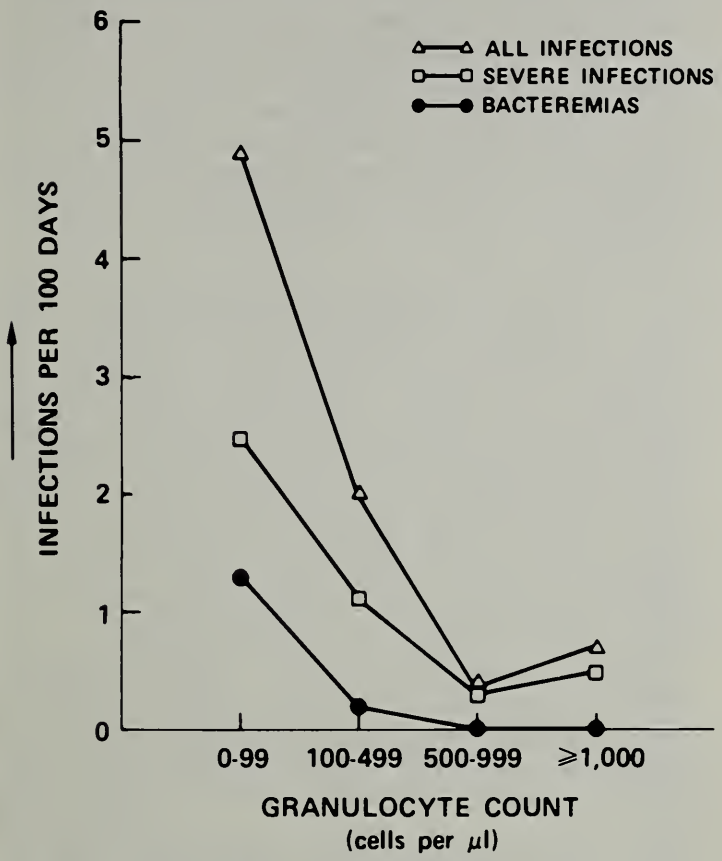

Figure 1.—Relationship of infection risk and granulocyte count in leukemia. (Reproduced with permission from Schimpff SC: Infections in the compromised host, *In* Mandell GL, Douglas RG Jr, Bennett JE [Eds]: Principles and Practice of Infectious Diseases, 2 vol. New York, John Wiley & Sons, sect B, chap 256, p 2259.)

cin against staphylococci and Gram-positive anaerobes, and nystatin against fungi). Because these agents were given orally and were not well absorbed into systemic circulation, this also reduced the risk of systemic toxicity (especially of the kidneys and ears) and superinfection.

Several prospective studies were conducted incorporating gentamicin, vancomycin and nystatin as the prophylactic regimen.[7,9,12] The results have varied from study to study, largely because of different experimental designs, but the following general conclusions can be made. First, there were conflicting data regarding the reduction of infection when nonabsorbable antibiotics were used orally in the absence of laminar air-flow units. For example, Levine and co-workers[7] and Yates and Holland[12] were unable to show a significant reduction of infection when these drugs were used without complete barrier isolation (see below). In contrast, Schimpff and associates[9] found a reduction in microbiologically recorded infection and infectious mortality with gentamicin, vancomycin and nystatin used in a routine ward setting. Second, therapy using this drug combination was very expensive, costing about $130 a day. Furthermore, the regimen was poorly tolerated by most patients and resulted in nausea, vomiting and diarrhea in many cases (generally attributable to vancomycin).[13] Consequently, the agents were often not taken continuously and many doses were omitted. Third, this poor patient compliance, in turn, led to the problem of recolonization of the gastrointestinal tract by resistant organisms (especially aerobic Gram-negative bacilli) that filled the microbial vacuum left by therapy with gentamicin, vancomycin and nystatin. Because these organisms were often multiply resistant, patient risk from infection may have actually been increased rather than decreased. Because of these problems with this drug regimen, alternative approaches to preventing infection in neutropenic cancer patients have been sought.

The next major advance in the use of prophylactic antimicrobial agents in neutropenic cancer patients came from two independent sources. In the late 1960s van der Waaij and colleagues[14,15] studied the mechanism(s) by which experimental animals were protected from gastrointestinal tract colonization with orally administered pathogenic Gram-negative bacilli. Through a number of experiments, they concluded that the presence of anaerobes tended to prevent gastrointestinal tract colonization by other challenge organisms. For example, in normal animals (mice), an orally given dose of about 10 million *Escherichia coli* was required for colonization. In germ-free animals, however, as few as 100 *E coli* could establish colonization. Animals that had been pretreated with antianaerobic agents were similarly at risk for colonization with small numbers of challenge *E coli*; in contrast, animals whose aerobic flora were eliminated with narrow-spectrum antimicrobial agents that preserved the anaerobic flora were relatively resistant to colonization. These experiments gave rise to the concepts of *colonization resistance,* that is, that maintenance of the normal anaerobic flora in the gastrointestinal tract might protect a neutropenic patient from being colonized with multiresistant and potentially pathogenic aerobic Gram-negative bacilli.

Prophylactic Use of Trimethoprim-Sulfamethoxazole

Meanwhile, studies were being conducted to assess the efficacy of trimethoprim-sulfamethoxazole (TMP-SMX) for preventing *Pneumocystis* infections in leukemic patients.[16,17] Hughes and colleagues[16] and Gurwith and associates,[17] in independent studies, established such efficacy. During these studies both groups of investigators unexpectedly found that in addition to abrogation of *Pneumocystis* infections, there was also a significant reduction in bacteremic infections in the trimethoprim-sulfamethoxazole-treated groups when compared with controls. It is especially noteworthy that in the latter study, little TMP-SMX resistance was found among fecal aerobic Gram-negative bacilli isolated after the prophylactic treatment. These data, in a ser-

endipitous way, supported the concept of colonization resistance. Since this time, several studies have examined TMP-SMX or similar agents for their ability to prevent infections in neutropenic cancer patients[18-21] (Table 1). Sleijfer and co-workers[18] used either oral TMP-SMX, colistin sulfate or nalidixic acid (depending on initial sensitivities of stool isolates on surveillance cultures) and found a reduction both in cases of bacteremia and in infection-related mortality when compared with patients not given prophylaxis. Dekker and colleagues,[19] using TMP-SMX as the prophylactic agent, also showed a decrease in cases of bacteremia and infection-related mortality; these were not statistically significant, however. The study of Weiser and associates[20] showed no significant prophylactic efficacy of orally given nonabsorbable antibiotic agents. This study was conducted in patients receiving maintenance chemotherapy, however, and patients were leukopenic for a very short period of time and were not critically ill, as were patients in the other studies. Finally, Wade and co-workers[21] compared patients receiving TMP-SMX plus nystatin with patients receiving gentamicin and nystatin orally. The two regimens appeared to be comparable in prophylactic efficacy. Of note, however, is that the TMP-SMX plus nystatin regimen was much less expensive ($5 a day versus $66 a day) and better tolerated.

Overall, then, the prophylactic use of trimethoprim-sulfamethoxazole appears to be promising. Many limitations do exist, however, and potential problems have arisen. For example, in the studies that yielded the best prophylactic results, serial multisite surveillance cultures were done to detect the emergence of resistant organisms during chemoprophylaxis. It is important to emphasize that once the gastrointestinal tract or other sites become colonized with TMP-SMX-resistant Gram-negative bacilli, it is not advisable to continue the use of this drug unless perhaps a second agent (for example, colistin) is added. Although in theory the maintenance of the anaerobic population should prevent the colonization by aerobic Gram-negative bacilli (as was the case in the study by Gurwith and colleagues[17]), in practice this does not always occur. Initial studies showed a very low incidence of emergence of resistant organisms with TMP-SMX therapy; however, several recent studies looking at TMP-SMX prophylaxis (both for prevention of urinary tract infections and for prevention of infections in immunocompromised hosts), have shown a potential for the development of resistance to either TMP-SMX or trimethoprim alone (Table 2).[22-25] Furthermore, in several neutropenic cancer patients bacteremias have developed due to TMP-SMX-resistant aerobic Gram-negative bacilli after they had received TMP-SMX prophylaxis.[24,25] Of particular concern is that several of the etiologic isolates also showed high-level resistance toward other clinically useful systemic antibiotic agents against Gram-negative bacillary infections (for example, ampicillin and aminoglycosides).

A second limitation to the use of TMP-SMX prophylaxis is that when neutropenic cancer patients become febrile, parenteral broad-spectrum antibiotic therapy is often empirically started; certain of these agents (for example, ticarcillin disodium) have a profound suppressive effect on the anaerobic flora of the gastrointestinal tract.[26] Once such systemic antibiotic treatment is initiated, it is no longer advisable to continue TMP-

TABLE 1.—*Efficacy of Trimethoprim-Sulfamethoxazole Prophylaxis in Neutropenic Cancer Patients*

Study	*Group*	*Number of Patients*	*Bacteremia* Number (Percent)	*Infection-Related Mortality (Percent)*
Gurwith et al, 1979[17]	Trimethoprim-sulfamethoxazole	59	0 (0)	4
	Control	52	9 (17)	16
Sleijfer et al, 1980[18]	Trimethoprim-sulfamethoxazole + nalidixic acid	53	3 (6)	0
	Control	52	8 (15)	11
Dekker et al, 1981[19]	Trimethoprim-sulfamethoxazole	33	4 (12)	16
	Control	33	7 (21)	20
Weiser et al, 1981[20]	Trimethoprim-sulfamethoxazole	33	1 (3)	0
	Control	34	2 (6)	0
Wade et al, 1981[21]	Trimethoprim-sulfamethoxazole	27	5 (19)	15
	Gentamicin-nystatin	26	8 (31)	31

TABLE 2.—*Trimethoprim-Sulfamethoxazole (TMP-SMX) Resistance in Patients Receiving TMP-SMX Prophylaxis*

Study	*Time Course Weeks*	*Site of Isolates*	*Extent of Resistance**
Guerrant et al, 1981[22]	4	Feces	Approx. 6 percent
Murray et al, 1982[23]	2	Feces	100 percent resistance to trimethoprim
Wilson et al, 1982[25]	approx. 2	Blood	In 2 patients bacteremia developed with TMP-SMX-resistant aerobic Gram-negative bacilli
Dekker et al, 1981[19]		Blood Feces	Fourfold higher rate of colonization with resistant Gram-negative bacilli; 2 episodes of fatal bacteremia due to TMP-SMX-resistant aerobic Gram-negative bacilli

*Among aerobic Gram-negative bacilli

TABLE 3.—*Guidelines for Use of Trimethoprim-Sulfamethoxazole (TMP-SMX) Prophylaxis*

Use only in those patients likely to have profound and prolonged (>21 days) neutropenia (for example, patients undergoing induction chemotherapy for acute myelogenous leukemia)
Do stool culture before therapy to screen for TMP-SMX resistance among aerobic Gram-negative bacilli
Repeat stool cultures twice a week on therapy; if TMP-SMX-resistant organisms emerge, consider adding a second agent to which isolates are sensitive (for example, colistin)
Discontinue prophylaxis when broad-spectrum systemic antibiotic drugs are administered

SMX prophylaxis unless perhaps the anaerobic flora can be reconstituted in some manner.[27]

In addition, it is felt by some investigators that TMP-SMX prophylaxis may not be appropriate when an underlying gastrointestinal or genitourinary tract or pulmonary malignancy is being treated because overgrowth by aerobic flora in these situations is undesirable and may give rise to anaerobic bacteremia.[28]

TMP-SMX cannot be considered a totally harmless medicine, as it may cause rash or other sulfonamide-type side effects in about 5 percent of patients.[29] Also, it is a systemically absorbed antibiotic and has the potential to obscure culture results, though this problem has not been reported in the medical literature. Finally, this drug combination may delay marrow recovery in neutropenic cancer patients due to its antifolate effect.

In what setting, then, should administration of TMP-SMX prophylaxis be considered? This question will undoubtedly require different answers in different institutions based on antibiotic resistance patterns, availability of laminar air-flow rooms and the accessibility of laboratory facilities for doing serial surveillance cultures. Broad guidelines that have been used in our institution are outlined in Table 3; these may prove to be applicable in many community or general hospitals in which the processing of serial multisite surveillance cultures by a clinical microbiology laboratory is impractical.

Before leaving the topic of antimicrobial prophylaxis, a comment on prophylaxis against fungal infections is in order. Although oral nystatin has been incorporated into most of the prophylactic regimens, there is little evidence that it reduces the incidence of serious fungal infection in neutropenic patients, though such a benefit has been reported in burn patients.[30] It may, however, reduce the frequency and severity of mucositis due to *Candida,* and this alone justifies its use. Experience with the newer antifungal agents in chemoprophylactic treatment of neutropenic cancer patients (for example, miconazole nitrate and ketoconazole) is limited.[31,32] There is agreement that prophylactic use of these agents does not reduce the incidence of colonization; whether or not the number of serious infections is reduced is unclear. One study[31] showed beneficial results when a dosage of 400 mg a day of ketoconazole was used; however, another study[32] found an increased number of fungal infections in the group receiving prophylaxis. A third study showed beneficial results in certain patients.[33] Clearly, further investigation will be required to clarify this issue. In the meantime, we would not advocate the routine prophylactic use of ketoconazole in neutropenic cancer patients.

The following are some simple, practical, but frequently overlooked, means by which infections can be reduced or prevented in a compromised patient.

Simple Prophylaxis

Immunizations

Very few killed vaccines are commercially available. (Live vaccines should be avoided because they may become virulent in compromised patients). Those killed vaccines that are available include influenzal and pneumococcal vaccines. We feel that both vaccines should be given even though pneumococcal pneumonia and influenza are responsible for a very small proportion of infections in neutropenic cancer patients and despite the fact that some of these patients are not able to mount an adequate immunologic response to the vaccine.[34] Passive immunization with a specific immunoglobulin is indicated in the appropriate exposure setting. The J5 vaccine, derived from a strain of *E coli,* is currently being studied by Braude and co-workers.[35,36] Both the vaccine and the antiserum obtained from patients hyperimmunized to this antigen show a great deal of promise. When the antiserum was given to animals that had experimentally induced *Pseudomonas* sepsis, death rates fell from 90 percent to 30 percent; similar improvements were observed in a small number of human patients. This gave rise to a study wherein leukopenic patients were given infusions of J5 antiserum every three weeks; a decrease in the number of febrile days was observed.[36] This promising development needs to be studied in further detail and in conjunction with other infection preventing modalities.

Strongyloidiasis

Patients with malignancy who have eosinophilia and those coming from areas where *Strongyloides* infections are endemic (for example, Southeast Asia, Mexico, southeastern United States) should have stool examinations for *Strongyloides* larvae before initiation of immunosuppressive therapy. This is important in neutropenic cancer patients because *Strongyloides* may rapidly reproduce in the gastrointestinal tract, resulting in the syndrome of "hyperinfection," in which larvae may widely disseminate, invading any organ system of the body, especially the lungs and the central nervous system. Other potential complications of this syndrome include bowel perforation or infarction, which would be especially catastrophic in these patients.

Instrumentation

A regrettably large number of infections in compromised patients apparently develops as a consequence of instrumentation. Much of this instrumentation is

necessary but some may be avoided. The use of urinary bladder catheters, for example, should be avoided in neutropenic cancer patients, except in cases of shock or outlet obstruction. All invasive diagnostic procedures should be done using meticulous sterile technique. The use of intravenous lines should be avoided when possible; if they are necessary, they should be placed with sterile technique, inspected daily and removed, if possible, within 48 hours. Steel needles may carry a lower risk of infection than Teflon catheters.[37] Intravenous lines and bottles should be changed daily, especially after administration of blood products, because blood products may not be sterile. When vascular access is problematic, placement of a Hickman or Broviac catheter should be considered.[38] Infectious complications are rarely associated with these lines,[39,40] and infections that do occur tend to be caused by organisms of relatively low pathogenicity, such as *Staphylococcus epidermidis.*

Hygiene

Finally, attention must be directed to proper hygiene. Patients should bathe and shampoo daily. Handwashing should be required of a patient and all those coming into contact with him. Povidone-iodine (Betadine)-impregnated swabs to axillary and perineal regions have been shown to reduce local infections.[41] Shaving of the axillary hair is to be discouraged. Good dental hygiene including brushing and flossing should be encouraged. Because periodontal disease is extremely common and is an important source of infections in neutropenic cancer patients, evaluation for oral surgical treatment before institution of chemotherapy is essential.[42]

Diet

Food is a common source of acquired potential pathogens, but a completely sterile diet is difficult to prepare in many hospital centers and is usually poorly tolerated by patients. A diet of low microbial content ("cooked food diet") should be used in neutropenic patients. Of particular importance is the elimination of green salads and ground pepper from the diet because of the heavy contamination of these food stuffs with aerobic Gram-negative bacilli such as *Pseudomonas.*

Dr Neil Barth will discuss other aspects of protective environments,[43] as well as granulocyte transfusions and other methods of immunopotentiation.

Providing a Protective Environment

NEIL M. BARTH, MD:* As noted by Dr Beutler, about 80 percent of infections in neutropenic cancer patients originate from endogenous microbial flora, and about 50 percent of the etiologic pathogens in infections occurring in these patients are acquired nosocomially.[4] These organisms colonize patients through contact with a wide variety of "vectors," including custodial or nursing personnel, physicians, other patients, medical instruments, air, food and water. Attempts at establishing protective environments have developed along two pathways: suppressing endogenous flora by prophylactic use of antibiotics and eliminating or limiting contact with the above-named vectors. Dr Beutler has already discussed antibiotic chemoprophylactic regimens for neutropenic patients.

The methods of decreasing colonization by hospital-acquired flora that have been examined with regard to neutropenic cancer patients cover the spectrum from simple protective isolation to the use of total protective environments.

"Simple protective isolation" is defined by the Centers for Disease Control as the physical isolation of a patient in a single-bed room with a private toilet and the use of a clean gown, gloves and mask by all persons entering the room. "Laminar air-flow" units refer to devices in which unidirectional (horizontal or vertical) air flow and air filtration of particles greater than 0.5 microns in diameter occur. These units may take the form of portable tents or permanent rooms and may be used with any combination of aseptic techniques with regard to a patient's personal hygiene, the immediate surrounding environment and the use of decontaminating procedures for skin, body orifices and gastrointestinal tract. The "life island" technique usually involves physically isolating a patient in a portable device in which the air is filtered by a high-efficiency particulate air filter, removing all particles of more than 0.5 microns in diameter, but lacking the laminar air flow in the environment. As in a laminar air-flow room, these units may be used with any combination of sterile techniques. Finally, "total protective environment" involves the application of four central elements: (1) physically isolating a patient in a room that has been completely sterilized; (2) using laminar air flow with a high-efficiency particulate air filtration system; (3) sterilizing all objects and personnel entering the room, including food and water, and (4) providing an aggressive program of gastrointestinal tract sterilization with administration of antibiotics, plus topical decontamination (for example, oropharynx and skin).

Published articles regarding the efficacy of each of these modalities in reducing the incidence of infections in neutropenic cancer patients are generally confounded by small study sizes, lack of adequate control groups and a wide variety of methods. The following general conclusions can be made, however, based on available data. Simple protective isolation has shown no benefit when used alone versus standard ward care in neutropenic patients, either in terms of infection rates or overall chemotherapy response rates or survival.[43,44] Also, simple protective isolation does not affect infection rates when used in combination with prophylactic antibiotics in such patients.[9,10,44] Laminar air-flow units or life islands have been examined by themselves as prophylactic modalities in only a small number of studies. These have shown that neutropenic cancer patients isolated in such units have a significant reduction in acquired staphylococcal, pseudomonal and respiratory viral infections.[45-48] In one study of 175 neutro-

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penic cancer patient admissions to laminar air-flow units, no cases of pulmonary aspergillosis, cryptococcosis or pneumocystosis occurred, whereas these infections were encountered elsewhere in the same institution.[45] Serious infections have still occurred, however, in neutropenic patients when in laminar air-flow units.[45]

The prophylactic effectiveness of total protective environments has been examined in 14 separate studies, of which less than half have been carefully controlled and randomized.[9,10,12,42-54] All except one of these studies[48] have shown a pronounced reduction (75 percent to 90 percent) in the incidence of serious infections in neutropenic cancer patients versus controls. Of note, this prophylactic efficacy was not generally observed until the third week of isolation in such units, perhaps reflecting the time required for complete decontamination to occur. However, serious infections still occurred in these units, and the etiologic organisms (*E coli, Candida, S aureus,* herpes, cytomegalovirus) were reflective of the inability by current methods to sterilize certain body sites (for example, the oropharynx) or to reduce latent viral infections.[55] A significant aspect of these units is the high construction costs (about $120,000 per unit) and the increased costs of various supportive services, such as for sterilizing food and water. It has been estimated that the cost of a six- to eight-week stay in such a unit during intensive induction therapy for acute leukemia is about $25,000 to $40,000.

One common goal in the use of any of the protected environments is to improve remission rates and to prolong life. In a small number of recent trials, chemotherapy drug doses have been escalated in conjunction with the use of protected environments. Early findings in patients who have solid tumors and hematologic malignancy have shown no significant differences in remission rates versus those in control patients. In addition, extramedullary toxicity (especially neurotoxicity or cardiotoxicity) seems to be the dose-limiting factor. In selected patient populations, however, such as children who have solid tumors, adding bone marrow reconstitution (via transplantation) to aggressive chemotherapy and protected environments has produced encouraging preliminary results.

Enhancing Patient-Host Defenses

Immunomodulation

Chemical immunomodulation has received considerable interest during the last several years. Lyman and associates,[56] by giving lithium carbonate during chemotherapy for small cell carcinoma of the lung, showed a significant decrease in myelosuppression and fewer infectious episodes versus that in control patients. In addition, infection-related mortality was lower in the lithium-treated group, and lithium-treated patients were able to receive higher cumulative doses of chemotherapy and had fewer treatment delays resulting from neutropenia.[56] The serious toxicity of lithium, including effects on the gastrointestinal tract and cardiac and renal systems, has dampened the clinical enthusiasm for this agent.

Nonspecific immune stimulants such as interferon, levamisole hydrochloride, bacille Calmette-Guérin vaccine, *Corynebacterium parvum* and cimetidine apparently require an intact cellular immune system to enhance the immune response.[57-59]

Nutritional Considerations

Nutritional assessment and support programs have only recently become popular in the care of neutropenic cancer patients. The use of such substances as hydrazine sulfate,[60] however, has improved glucose metabolism in patients with underlying neoplasia. Of interest, anergic patients with neoplastic disorders who are severely malnourished have had reversal of cutaneous reactivity through using only nutritional support (for example, hyperalimentation).

Granulocyte Transfusions

Granulocyte (leukocyte) procurement and transfusion procedures are well established and generally within the financial and technical scopes of most modern community and university hospitals. However, the clinical experience gained with granulocyte transfusions in neutropenic patients has shown that there may be only a small subset of patients who benefit from this procedure.

There are currently two widely used techniques for harvesting leukocytes for transfusion. The older and more accepted technique is *continuous flow centrifugation.* This technique uses the principle of variable sedimentation rates in a standard gradient to yield three cell fractions and cell-free plasma. The leukocyte fraction is collected separately and the remaining fractions reinfused into the donor. The newer technique, *continuous flow filtration,* utilizes leukocyte adherence to nylon. After afferent blood flow is terminated, leukocytes adhering to nylon filters are collected and residual cells returned to the donor. The efficiency of the continuous flow filtration is about fourfold greater than that of the centrifugation method; however, donor thrombocytopenia and the decreased survival of transfused leukocytes are potential problems. The average number of leukocytes collected by either method is approximately 0.5 to 20 billion cells; this is about a third the number necessary to raise peripheral blood leukocyte counts in a normal adult from 0 to about 5,000 per μl. Additionally, it has been shown by in vitro assays that harvested leukocytes retain their phagocytic and bactericidal properties, as well as normal intact chemotaxis.[61,62]

Two factors that may adversely affect leukocyte survival in a recipient are the presence of natural or acquired leukoagglutinins and the posttransfusional development of cytotoxic antibodies directed against granulocytic membrane antigens. Also, the lack of shared human leukocyte antigenicity between donor

TABLE 4.—*Studies of Therapeutic Leukocyte Transfusions for Infections During Induction Chemotherapy*

Study	Entry Criteria: Peripheral Neutrophil Count × 10^9/liter	Entry Criteria: Relation to Infection	Transfusion Data: Collection Method	Transfusion Data: Days Transfused Median (Range)	Response to Therapy/Survival: Control (Antibiotics Only)	Response to Therapy/Survival: Antibiotics Plus WBC Transfusions
Higby et al, 1975[67]	< 500	Receiving antibiotics for >2 days without improvement	CFF	4	4/12	10/11
Fortuny et al, 1975[65]	< 500	>48 hrs nonresponse to antibiotics for culture-proved infection	CFC	4	12/17	15/21
Vogler and Winton, 1977[70]	< 300	>72 hrs nonresponse to appropriate antibiotic therapy for culture-proved infection	CFC	7 (2 to 17)	1/8	6/9
Alavi et al, 1977[68]	< 250	36 hrs after onset of febrile episode	CFF	7 (3 to 18)	10/19	11/14
Herzig et al, 1977[69]	<1,000	Within 24 hrs of blood cultures being positive	CFC vs CFF	9 (5 to 42)	5/14	12/16
Winston et al, 1982[71]	< 500	Within 24 hrs of 'documented' infection	Discontinuous flow centrifugation	12 (2 to 62)	23/36	19/32

CFF = continuous flow filtration; CFC = continuous flow centrifugation; WBC = leukocyte.

*Survival to day 21 postinduction.

and recipient has been associated with impaired leukocyte survival posttransfusion.

The average cost to a patient for a single leukocyte transfusion is around $800 to $1,200. Because "therapeutic" leukocyte transfusions (given for an established infection) are generally administered for about four to ten days, whereas "prophylactic" transfusions are often given for longer periods, the cost is considerable.[63]

Therapeutic Leukocyte Transfusions

Early efficacy studies of therapeutic leukocyte transfusions in small populations of neutropenic cancer patients showed a statistical benefit in terms of survival versus that in untransfused patients (Table 4).[64-70] These trials generally selected a patient "survival" of 21 days as an endpoint, that is, the time of expected bone marrow recovery from cyclic chemotherapy. When one further analyzes the data from the earlier studies of therapeutic leukocyte transfusions in neutropenic patients, certain predictive prognostic factors can be delineated. Those patients with culture-documented bacterial or fungal infection and those patients who had profound, protracted granulocytopenia without marrow recovery seemed to show survival benefit from leukocyte transfusions (about 75 percent versus 20 percent in controls). In contrast, benefit could not be demonstrated in transfused neutropenic patients with febrile episodes of undetermined origin or those whose marrow recovered within a 21-day period (or both groups). A recent controlled trial by Winston and co-workers[71] of the use of therapeutic leukocyte transfusions in 95 episodes of documented infection in neutropenic cancer patients has placed this entire subject into clear perspective. These investigators could find no substantial survival benefit of therapeutic leukocyte transfusions in their patients over optimal antimicrobial therapy alone. Also, as opposed to previous trials that had found benefit from the therapeutic granulocyte transfusions in the subset of patients with Gram-negative bacteremia and prolonged marrow aplasia, no such benefit was noted in the study of Winston and colleagues.[71]

Prophylactic Leukocyte Transfusions

Prophylactic leukocyte transfusions (that is, given to neutropenic patients before the onset of febrile episodes) have not been of consistent benefit to any subset of these patients.[63,64,72-77] Although multiple studies in the early 1970s showed a decrease in infectious episodes in the transfused versus control populations, these reports are difficult to compare and interpret because of the great variety in study designs and methods; also, a true assessment of the risk-benefit ratio of prophylactic leukocyte transfusions could not be obtained. In an effort to clarify this matter, the National Heart, Lung and Blood Institute recently conducted a cooperative multicenter study involving 102 adults undergoing induction chemotherapy for acute myeloblastic leukemia who were prospectively selected at random either to receive prophylactic leukocyte transfusions or to be part of a control untransfused population.[78] The following conclusions were reached after data analysis: there was no significant difference in the overall incidence of recorded infections between control and transfused groups; there appeared to be a higher percentage of bacterial infections in the control population versus a much higher incidence of pneumonia of undetermined cause in the transfused group; prophylactic leukocyte transfusions did not delay the time to clinical onset of infection, with a median time of 7 to 21 days for first appearance of febrile episodes, in each study group; prophylactic transfusions produced no significant effects on bone marrow recovery times or remission induction, and the overall mortality of transfused patients was nearly twice that of controls.

In addition to any questionable benefits of prophy-

TABLE 5.—*Major Complications of Granulocyte Transfusions*

Systemic constitutional reactions
Alloimmunization
Pulmonary reactions
Graft versus host disease
Cytomegalovirus infection

lactic leukocyte transfusions, the adverse side effects of all such transfusions must be considered (Table 5). Systemic toxicity was a significant problem in the cooperative study mentioned above.[78] For example, 72 percent of transfused patients showed some adverse effect; in about half fever and chills developed following the transfusion and 20 percent had dyspnea or wheezing. In 10 percent of the patients, transfusions had to be discontinued because of the severity of systemic side effects.

Immunization to leukocytic membrane antigens occurs in about 80 percent of transfused patients.[78-81] Because of shared antigens on both platelets and leukocytes, patients who become alloimmunized from leukocyte transfusions may become cross-alloimmunized to platelet transfusions, making this replacement modality problematic. Also, graft versus host disease has been reported in patients receiving multiple leukocyte transfusions because of the burden of immunocompetent lymphocytes that may be delivered during successive transfusions.[62]

Pulmonary toxicity has been a relatively common and serious complication of leukocyte transfusions and is associated with about a 35 percent mortality.[78] Postulated mechanisms for pulmonary reactions during leukocyte transfusions include fluid overload, sequestration of transfused leukocytes in extensive pulmonary lesions and release of vasoactive amines from the interaction of leukocytes and circulating endotoxins.[78] Leukoagglutinins causing intravascular leukocyte aggregation and subsequent embolization to the lungs, or the direct transfusion of aggregated leukocytes, is thought to cause the most severe pulmonary reaction resulting in refractory pulmonary edema.[82] Worsening of the pulmonary toxicity associated with leukocyte transfusions has been reported to occur with concomitant amphotericin B administration.[83] Although the correlation is not firmly established, if both modalities are being used, it is recommended that their administration be temporally separated by 6 to 12 hours.[83]

Another serious complication noted in reported series of neutropenic cancer patients given prophylactic leukocyte transfusions is cytomegalovirus infection.[65] In a study from the UCLA Medical Center of prophylactic leukocyte transfusions, the incidence of cytomegalovirus infection, particularly interstitial pneumonia, was significantly higher in a transfused (versus control) group of neutropenic cancer patients.[84] Furthermore, the presence of elevated cytomegalovirus antibody titers before transfusion apparently did not protect against developing posttransfusional cytomegalovirus infection.

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Medical Staff Conference

Pemphigus

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR RECTOR:* *The topic of this Medical Staff Conference is pemphigus. Dr Charles Simonton will present the summary of the case to be discussed.*

Report of a Case

DR SIMONTON:† The patient was admitted in mid-September and died in mid-November 1982. This was the first University of California, San Francisco, admission for this 68-year-old woman. She had a three-year history of pemphigus vulgaris and was admitted for intensive local skin care and systemic therapy for her progressive pemphigus.

Her problems began in January 1979, when she was first seen in the Dermatology Clinic because of oral ulcers for 2½ months, treated with topical lidocaine (Xylocaine) and penicillin. Her only other medicines at that time were vitamins B and C. She had no history or family history of skin disease and no history of Raynaud's phenomena, joint pains, urethritis, conjunctivitis, inflammatory bowel disease or any cardiorespiratory disease.

On physical examination erosive white lesions on the tongue and buccal mucosa (Figure 1) were noted, as well as eroded areas of the left side of the vulva. An antinuclear antibody test at that time was positive at a titer of 1:40 with a speckled pattern, the triiodothyronine (T_3) level was normal, a VDRL was negative and a complete blood count showed no abnormalities. A biopsy specimen of one of the mucosal lesions had changes typical of pemphigus. She also had positive direct immunofluorescence, but negative indirect immunofluorescent staining of the biopsy specimen. Administration of 60 mg of prednisone per day by mouth was started, which was decreased over several weeks to 20 mg, alternating with 5 mg, daily. In April 1979 the prednisone dose was increased to 50 to 60 mg a day because of relapsing oral lesions. In addition, she was given topical fluocinonide (Topsyn) and intralesional steroid injections. By May 1982 medication had been reduced to 10 mg of prednisone every other day and the disease was stable. She then had a flare-up of oral lesions and the prednisone dose was increased to 20 mg daily.

For the first time skin lesions involving the neck, chest, vagina, labia and upper back developed, which subsequently became some of her most difficult areas to manage (Figure 2). Pemphigus antibody test at that time was positive, and the prednisone dosage was increased to 60 mg a day. Despite an increased amount of prednisone, she had to be admitted to the Dermatology Service for persistent disease in the mouth and large bullae over the upper back and neck. The cultures of those lesions grew out *Proteus* and *Staphylococcus aureus;* prednisone was further increased to 80 mg a day and she was given dapsone, 25 mg a day—subsequently increased to 75 mg a day—and dicloxacillin. During this time numerous complications related to taking steroids developed, including fasting hyperglycemia. She in addition became anemic, which was thought to be due to chronic disease, had mildly guaiac-positive stools and also had quite a bit of blood oozing from her skin disease. New bullous lesions developed in October, with a positive Nikolsky's sign: applying pressure to the skin with lateral motion caused the superficial epidermis to come off. There was also lack of healing of other areas; her prednisone dose was therefore increased to 100 mg a day, intramuscular administration of methotrexate, 50 mg a week, was begun and the dapsone therapy was discontinued. Her local skin care continued with Opsite applied to all affected areas, being changed every 72 hours with very attentive wound care by a specialist. Her appetite diminished and dysphagia and dyspepsia developed. Plasmapheresis was considered as an alternative therapy, but was postponed because the skin lesions appeared to be getting stable on administration

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†Charles Simonton, MD, first-year resident.

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of higher dose steroids. At this time depression and steroid-induced mental status changes also developed.

She underwent endoscopy by a gastroenterology consultant that showed three forms of diffuse panesophagitis: pemphigous involvement of her esophagus and monilial and herpetic esophagitis. She was given antacids and nystatin. Then spiking fever to 38°C (100.4°F) developed and cultures of blood and cerebrospinal fluid specimens were done. Her leukocyte count was 4,300 per cu mm and cultures were negative. Cultures of specimens from the skin erosions grew *Pseudomonas, Klebsiella* and *Proteus* spp, and antibiotic administration was begun. Her mental state began to worsen, there was more disorientation and she had a great deal of pain during dressing changes. Administration of antibiotics was then stopped due to negative results of cultures. Her skin lesions had some small areas of reepithelization and large doses of analgesics were needed for pain. Next a *Pseudomonas* urinary tract infection developed and she was given appropriate antibiotic therapy, with a subsequent drop in her temperature. Her skin lesions were not healing with Opsite, but new lesions were not occurring and she was receiving prednisone, 50 mg alternating with 30 mg a day.

Figure 1.—Oral mucosal erosions in a 68-year-old woman with pemphigus.

The patient was transferred to our service for plasmapheresis in early November, and had treatment for three days in a row. She had severe wound infection and areas of cellulitis for the first time. An erosion began to develop that penetrated to subcutaneous fat and was exudative. She was again started on antibiotic therapy to treat the possible sepsis and cellulitis, given her multimicrobial superinfection. She appeared critically ill, was confused and a cough developed. A chest roentgenogram showed a right middle lobe infiltrate, progressing to fluffy upper lobe infiltrates as well. She had her second trial of plasmapheresis and cyclophosphamide therapy was begun. She continued to be febrile and the regimen of antibiotics was changed to extremely broad coverage agents; this was discontinued in two days because of lack of response.

Diffuse areas of ecchymosis with normal coagulation times then developed, with recurrent fever and increasing upper lobe infiltrates, despite negative results on cultures. Antibiotic administration was stopped and

Figure 2.—Multiple large superficial blisters and erosions of the skin of the upper back of same patient as in Figure 1.

TABLE 1.—*Classification of Various Types of Pemphigus*

Pemphigus vulgaris	Brazilian pemphigus
Pemphigus foliaceus	Patients with overlapping types
Pemphigus erythematosus	
Pemphigus vegetans	Childhood pemphigus

Figure 3.—Chinese herbal treatment of pemphigus. "Dog skin" ointment has been applied to areas covered by plasters.

she received her fourth treatment of plasmapheresis. In addition, acute rectal bleeding developed that on sigmoidoscopy appeared to be due to a rectal mucosal ulcer. Her prothrombin time then started to go up to 15.2 seconds, with a partial thromboplastin time of 46.1 seconds, her platelet count was stable and her hematocrit dropped to 22 percent. She was transfused with fresh frozen plasma and packed red cells, and it was felt that she might have low-grade intravascular coagulation, though her fibrin-split products were only minimally elevated. In mid-November she had her fifth trial of plasmapheresis, but due to her severe disorientation and poor prognosis, a multiteam conference was held in which it was decided not to initiate mechanical cardiopulmonary resuscitation should she have an acute decline. Later that afternoon she had a massive upper gastrointestinal bleed with aspiration and died.

Postmortem examination showed numerous ulcerated skin lesions, areas of mucosal hemorrhage without any definitive lesions, esophageal ulcerations and the rectal mucosal ulcer. In addition, there were bilateral pleural effusions, blood throughout the bronchial tree from aspiration, some intraparenchymal hemorrhage and a possible pulmonary embolus.

DR RECTOR: *Thank you, Dr Simonton. I think this case shows what a disastrous disease pemphigus can be. Management of its complicated problems stresses the skills of physicians. We are very fortunate to have with us Dr Denny Tuffanelli, who is Clinical Professor of Dermatology at the University of California, San Francisco.*

Discussion

DR TUFFANELLI:* In the past 15 years there have been several major advances in our understanding of the chronic immunologic blistering diseases. The classic bullous diseases include pemphigus, pemphigoid, dermatitis herpetiformis, erythema multiforme and their variants. The case presented here gives us an opportunity to discuss some of these advances. Pemphigus is an autoimmune disease. In many respects it is quite similar in pathogenesis to myasthenia gravis and Goodpasture's syndrome and its pathogenesis is probably related to IgG antibodies. We now have the technology to determine the molecular structure of the antigens with which pemphigus antibody reacts. Moreover, it is possible that therapy directed towards removing the antibody will be beneficial.

Historically, pemphigus has been classified into various types (Table 1). These include vulgaris—the commonest form, foliaceus, erythematosus and vegetans. At least three of these forms have definitely different antigen-antibody patterns. Another variant, Brazilian pemphigus, is an infectious disease prevalent in Brazil and neighboring countries. It is transmitted by an arthropod-borne vector. Patients who have this disease have the pemphigus antibody, as do their family members and relatives.[1]

Pemphigus vulgaris is the classic form of pemphigus. It is characterized by flaccid blisters occurring on normal skin. Mucous membrane including the esophagus can be affected.[2] Acantholysis of epidermal cells leads to erosions and blisters. It occurs most frequently in Jewish people, particularly Ashkenazi (eastern European), and has an association with HLA-A10 antigen. In my personal experience in San Francisco, which may be clinically biased, pemphigus is more common in Chinese persons. The patient shown in Figure 3 has pemphigus being controlled with low doses of corticosteroids. He also uses Chinese herbs under plasters as treatment. This practice is fairly common in older Chinese. The particular herb he uses is "dog skin" ointment. It has nothing to do with dog skin but strong names, for example, "tiger balm," are deemed important. In any event, the disease in San Francisco is as common in Chinese as in Ashkenazi Jews.

The foliaceus form is different antigenically. Histologically the blister is in the upper layers of the epidermis, and the antigen with which the antibody reacts is also found high in the epidermis.[3] Patients with pemphigus erythematosus have features of pemphigus foliaceus and lupus erythematosus.[4] About 30 percent are positive for antinuclear antibody; many have a positive linear deposition of IgG at the dermoepidermal junction, and many have clinical features of systemic lupus erythematosus. Thus the three major forms of

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pemphigus all apparently have different antigens and antibodies involved in the pathogenesis.

Pemphigus usually begins, as in this patient, with oral erosions. About 50 percent to 60 percent of patients present with oral lesions and in 96 percent oral lesions will eventually develop.[5] The disease usually disseminates about four or five months later, though in this patient it was almost three years. In a patient who has chronic mouth erosions, one must always consider the chronic blistering diseases. Often the only way to make a diagnosis is by biopsy for direct immunofluorescence. Frequently blisters are not present, and routine biopsy is not diagnostic. Early in the course of the disease, patients frequently do not have circulating antibodies.[5] Thus one must take a biopsy specimen of normal oral mucosa adjacent to an erosion for immunopathology. Direct immunofluorescence will show the diagnostic antibodies if they are present.[6]

The biopsy specimen from this patient's oral mucosa, stained with a fluorescein-labeled anti-IgG, is shown in Figure 4. She had been observed for three months before the disease was diagnosed and had been seen by several physicians. We saw her in a morning clinic, did the biopsy and staining and had the diagnosis by that afternoon. This is a very simple procedure that should be used routinely in patients with chronic oral erosions. There are a large number of the chronic oral erosive diseases and in many of them the diagnosis is best made by immunopathologic tests.

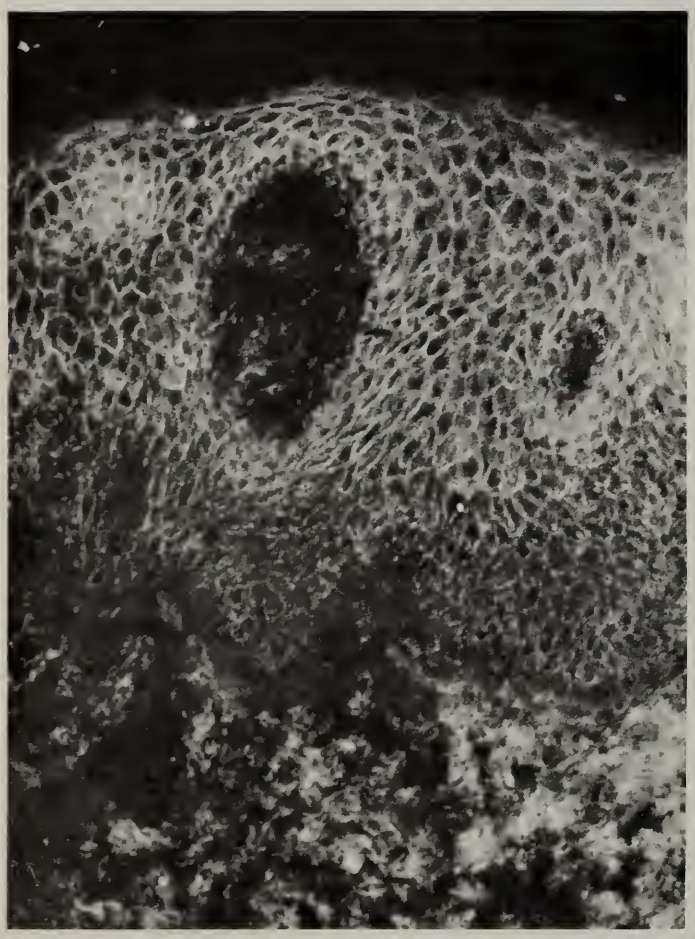

Figure 4.—Direct immunofluorescence of skin biopsy specimen of patient presented here. Following staining with fluorescein-labeled anti-IgG, intercellular deposition of antibody can be seen.

TABLE 2.—*Indications in Dermatologic Disorders for Immunopathology Studies*

Lupus erythematosus and variants
Diagnosis
Prognosis
Light-sensitive disorders
Mixed connective tissue disease
Chronic bullous disease
Pemphigus
Pemphigoid
Dermatitis herpetiformis
Acquired epidermolysis bullosa
Chronic erythema multiforme
Cutaneous vasculitis
Cutaneous porphyrias
Scarring alopecia
Erosive mouth lesions

Routine pathology studies in pemphigus classically show a bulla in the epidermis. In pemphigus vulgaris it is located in the lower epidermis and in pemphigus foliaceus in the upper epidermis. Because of loss of cell-to-cell attachments, one sees acantholytic (rounded up) epidermal cells in the bullae.

There are many indications for immunopathologic studies in dermatologic cases (Table 2). Our laboratory has processed over 10,500 slides. In many instances immunopathologic examination should be done for the diagnosis of lupus erythematosus, the photosensitive skin disorders, chronic blistering diseases, cutaneous vasculitis, scarring alopecias and erosive mouth lesions.

In a specimen of a perilesional skin biopsy of a patient who has pemphigus one can see deposition of IgG in the intracellular area. By indirect immunofluorescence, a patient's serum that is placed over monkey esophagus (which is used as a stratified squamous epithelium substrate) will show circulating intercellular antibody (Figure 5).[7] This patient did not have detectable circulating antibodies for the first three years of her disease. When her disease ultimately flared a high titer circulating antibody developed. Table 3 shows the pemphigus data that we have generated over the years. From 80 percent to 90 percent of patients with the various forms of pemphigus have epidermal deposition of antibody. The serum studies are slightly less sensitive for diagnosis than are the biopsy studies.

The disease activity in general relates to antibody titer.[7] Patients who have high titer antibody levels usually have very active disease. As their antibody titer decreases, their disease clinically goes into remission.

Pemphigus can be induced by external agents. Penicillamine is the drug that most commonly induces pemphigus. There are over 48 cases in the literature in which pemphigus, usually of the foliaceus type, has been induced by penicillamine.[8] Both circulating and bound intercellular antibodies are found. In about half of these patients the disease will disappear when the

drug therapy is discontinued. It is one of the major problems related to penicillamine therapy. Captopril is another drug that recently has been reported to induce pemphigus-like antibodies and a blistering disease similar to pemphigus.[9] Captopril has a chemical structure very similar to that of penicillamine.

Clues to the cause of pemphigus are of great interest at this time. We recently observed a pregnant patient who was being given azathioprine and prednisone for treatment of pemphigus. She had a stillborn fetus that had macerated skin lesions. A skin biopsy specimen of the fetus showed deposition of intercellular substance antibody. A similar case[10] and a case of neonatal pemphigus in which the mother had pemphigus[11] have been reported.

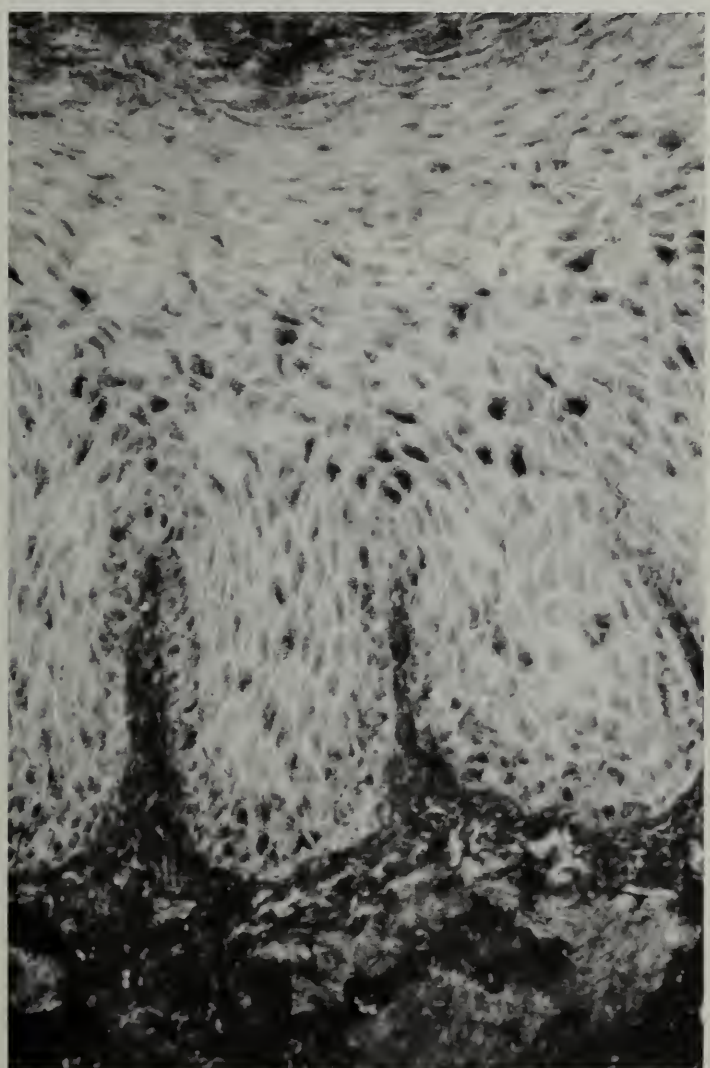

Figure 5.—Indirect immunofluorescence, using monkey esophagus as substrate, shows circulating intercellular antibody.

TABLE 3.—*Results of Immunopathology Studies in Patients With Pemphigus*

Diagnosis	*Biopsy Done No. of Patients*	*Percent Positive*	*Sera Studied No. of Patients*	*Percent Positive*
Pemphigus vulgaris	150	85	160	74
Pemphigus foliaceus	14	71	12	50
Pemphigus erythematosus ..	8	100	8	75

There have been many studies on the pathogenesis of pemphigus. Pemphigus antibody binds to the surface of human epidermal cells. Pemphigus antibody injected into a monkey binds with the intercellular antigen in the skin and produces acantholysis. Epidermal acantholysis occurs in normal human explants cultured in vitro with pemphigus IgG.[12] Complement and inflammatory cells are not required. The acantholysis can be prevented by administering serine protease inhibitors.[13] An early ultrastructural change is loss of the glycocalyx between epidermal cells.[14] A current concept of pathogenesis is that pemphigus antibody induces epidermal cells to activate cellular serine proteases which degrade the glycocalyx and induce acantholysis.[15] By electron microscopy one can see in early lesions widening of the intercellular spaces and dissolution of intercellular cement. The cellular attachments, desmosomes and tonofilaments, seem to be intact. In studies using immunoelectron microscopy, the antibody has been reported to be both in the intercellular space and on the keratinocyte surface, particularly in the desmosome-tonofilament area.[16] In summary, the pemphigus antibody is bound to cell membrane; enzymes are released by the epithelial cells, which leads to dissolution of the intercellular space, retraction of the tonofilaments and loss of the desmosomes. Acantholysis occurs and the blisters develop.

Currently there is a great deal of interest in the antigen(s) of pemphigus. To characterize the antigen(s) radiolabeled keratinocyte cultures were immunoprecipitated with sera from patients with pemphigus.[17] In five of seven of the cultures the antigen precipitated was a 130-kilodalton molecule to which the pemphigus antibody was attaching. We are in the process of restudying (in Dr Kimie Fukuyama's laboratory) this patient's serum, using as antigen epithelial cells extracted with different solvents. Apparently the patient had at least two antibodies reacting with keratin antigens and several other pemphigus IgG antibodies reacting with several different epithelial antigens. Certainly the technology for these studies is available. We should soon have a good idea of what the pemphigus antigen(s) is.

Pemphigus has recently been induced in neonatal mice by passive transfer of IgG antibodies from patients with disease.[18] Following IgG fractions administered intraperitoneally, cutaneous blisters developed in these mice with the histologic, ultrastructural and immunofluorescent features of pemphigus.

Differential Diagnosis

I will next discuss the differential diagnosis of the chronic blistering diseases and point out some of the immunologic advances that have occurred in our understanding of these diseases. Bullous pemphigoid is often difficult to differentiate from pemphigus on clinical grounds alone. The blister of bullous pemphigoid is subepidermal, however. Immunopathologic examination shows the antibody IgG and complement to be deposited in a linear fashion at the dermoepidermal junction. Pemphigoid sera contain circulating antibody

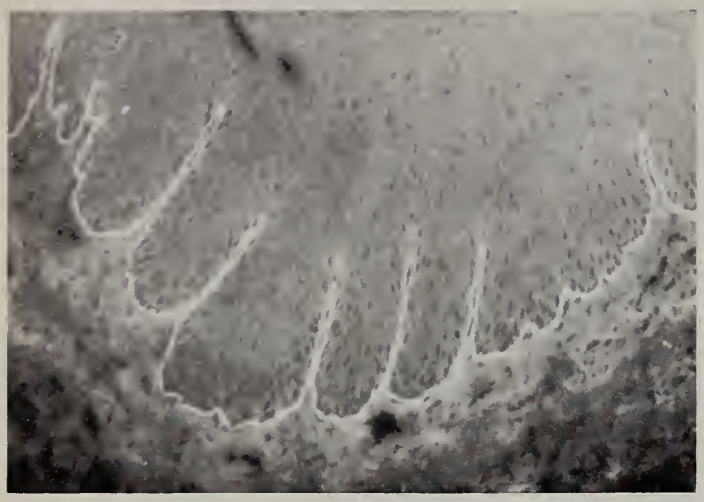

Figure 6—Immunopathologic studies in a case of bullous pemphigoid, showing circulating basement membrane zone antibodies.

to the basement membrane zone (Figure 6). Cicatricial pemphigoid is a pemphigoid variant in which patients have primarily mucous membrane involvement, including conjunctival oral, esophageal, vaginal and perianal lesions. They also often have cutaneous lesions. Immunopathologic studies of cicatricial pemphigoid show IgG and complement at the dermoepidermal junction (Figure 7), but these patients usually do not have circulating antibodies, whereas patients with bullous pemphigoid do. Acquired epidermolysis bullosa is a disease that clinically, histologically and immunopathologically resembles cicatricial pemphigoid. Pronounced scarring of the hands due to chronic blistering and esophageal and tracheal involvement with scarring can occur. However, electron microscopy can differentiate these diseases. In patients with the various forms of pemphigoid, antibody is deposited and the bullae occur in the lamina lucidum of the basement membrane zone. In acquired epidermolysis bullosa, the anchoring fibrils that attach the dermis to the basal cells are absent or decreased, and the antibody appears to attach to the anchoring fibrils.

Dermatitis herpetiformis presents with chronic, pruritic, vesicobullous lesions. These patients have IgA depositions in the skin and gut and often exhibit the HLA-B8 antigen. Many have a gluten-sensitive enteropathy. Pathologic examination of dermatitis herpetiformis lesions shows features closely resembling those of the pemphigoids. However, the immunopathologic appearance is distinctive, showing a granular deposition of IgA in the dermal papillae. A variant of classical dermatitis herpetiformis are so-called linear IgA dermatoses. Clinically, these patients have features of both dermatitis herpetiformis and pemphigoid. Patients who have the classic form of dermatitis herpetiformis and granular IgA deposits respond promptly to therapy with dapsone. The patients with linear IgA depositions rarely have gluten-sensitive gastroenteropathy. Linear IgA dermatoses and all the chronic bullous diseases occur in children.

Treatment

Finally, a few words about management and therapy. Pemphigus is a disease that rarely responds to a simple approach. Many patients, as this patient for the first two or three years of her disease, do extremely well. Other patients, as was the case with this patient in the last few months of her disease, have catastrophic problems. Before the use of corticosteroid therapy the mortality of pemphigus was 90 percent.[19] This figure has been steadily dropping and the mortality of pemphigus now ranges from 10 percent to 15 percent. The morbidity rates are high when patients are given systemic corticosteroids for a prolonged period. Management of necessity includes corticosteroids as the drugs most commonly used.[20] Side effects are a major problem. There is no good evidence for which of the immunosuppressants is of most use if steroids do not control the disease. All can be used with corticosteroids. Methotrexate use can cause oral ulcerations, a major problem in pemphigus patients who have mucosal lesions.[21] The use of cyclophosphamide poses numerous problems including those of sterility and hemorrhagic cystitis. Azathioprine has not been used very much. Gold

Figure 7.—Immunopathologic studies in a case of cicatricial pemphigoid. Skin biopsy specimen shows deposition of IgG antibody in the basement membrane zone.

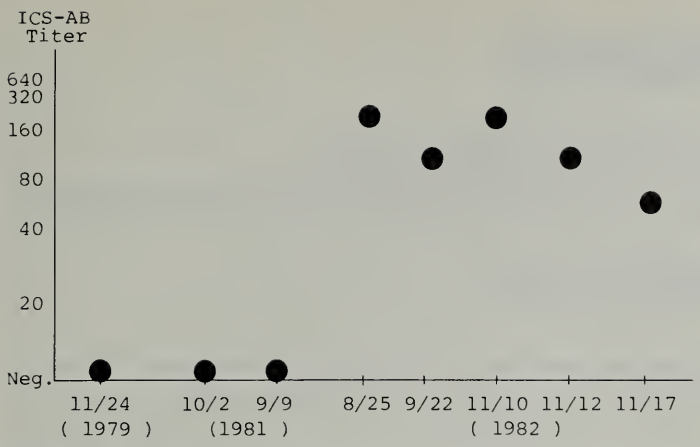

Figure 8.—Time course of antibody levels in patient discussed here. ICS-AB = intercellular substance antibody.

sodium thiomalate[22] is being given but certainly would not be useful in a patient with explosive and overwhelming pemphigus. Dapsone is a reasonably safe drug that can be added to this list. As we mentioned, it works extremely well in the treatment of dermatitis herpetiformis. It has been used, as it was in this patient, in hopes of decreasing steroid side effects. Dapsone probably has a role, particularly in elderly patients with mild disease who do not tolerate steroids well. Plasmapheresis is a newer therapy that has been sporadically utilized in an attempt to reduce the titer of pemphigus antibodies.[23,24] In a recent study of 11 patients treated with plasma exchange the antibody titers decreased promptly, and clinically there was a good response.[25] There was a frequent rebound in antibody synthesis after 14 days. Therefore, one needs to give patients steroids and immunosuppressives to prevent the rebound synthesis of antibodies. We will not discuss extensively the side effects of plasmapheresis. Certainly the removal of IgG, IgM and IgA antibody leads to immunosuppression, and a depletive coagulopathy can occur.[26] Further, immunosuppressive therapy is necessary to prevent antibody rebound. There are major problems with the long-term use of plasmapheresis in the treatment of pemphigus such that it may or may not ultimately have a role.

Summary

We have discussed pemphigus, particularly the clinical importance of autoantibodies in this disorder. The pemphigus antibody plays a role in pathogenesis of the disease. When patients have mild disease, they have a low titer antibody level. When they have severe disease, they have high antibody levels.[27] Removing the antibody likely is therapeutically beneficial. The antibody probably relates directly to pathogenesis and is not an epiphenomenon. Major questions remain unanswered. Do antibody levels per se have prognostic and therapeutic implications? Can one predict an exacerbation of the disease if antibody levels rise? And, more importantly, can one prevent a flare-up of the disease if one treats a patient who has a rising antibody titer but no clinical evidence of activity? There are simply no data on this point.

Figure 8 shows the antibody studies from the patient discussed here. When we first saw this patient the diagnosis was made clinically and by the presence of intercellular IgG in the biopsy specimen from her mucous membrane. She did not have measurable circulating antibody for the first three years of her disease. When the dose of prednisone was reduced to 10 mg every other day, she had a clinical flare-up. There was a coincident high titer of her antibody. We were able to lower her antibody level somewhat by plasmapheresis, but it was too little and too late. As I think about this patient, I have two quesions: If we had been following her antibody levels, could we have predicted her clinical flare? If we had found a rise in antibody titer and elected to treat that, could we have prevented the disease flare? I do not know the answer to these questions—nor does anyone else at this time.

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Epitomes

Important Advances in Clinical Medicine

Internal Medicine

The Scientific Board of the California Medical Association presents the following inventory of items of progress in internal medicine. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers or scholars to stay abreast of these items of progress in internal medicine that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Internal Medicine of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Pulmonary Sarcoidosis: Indications for Treatment

PATIENTS WITH PULMONARY SARCOIDOSIS in whom the disease is confined to the hilar and mediastinal nodes (stage I) seldom require specific therapy. In patients with progressive pulmonary involvement, however, corticosteroid therapy is almost always indicated. Controversy surrounds the treatment of those patients who are either asymptomatic or have minimal symptoms but who show radiographic evidence of persistent, stable pulmonary infiltrate. Some authorities believe that corticosteroids should be used in such cases only in the presence of symptoms such as dyspnea, intractable dry cough and the like, or with evidence of worsening lung function—for example, severely reduced diffusing capacity, hypoxemia, exercise intolerance and so forth. Others contend that all patients who have pulmonary infiltrates (stages II and III) are candidates for corticosteroid therapy. This difference of opinion stems from the fact that the conventional methods (history and physical examination, chest radiography and lung function tests) of assessing the activity and prognosis of sarcoidosis have not proved consistently reliable. The recent development of the following three techniques as markers of disease activity has made it possible to identify those patients who require treatment.

Serum angiotensin-converting enzyme level is raised in about 60 percent of sarcoidosis patients. The test is not specific for sarcoidosis as levels may be elevated in silicosis, miliary tuberculosis, primary biliary cirrhosis, leprosy, coccidioidomycosis, hypersensitivity pneumonitis, chronic liver disease, lymphoma and diabetes. Its value, however, lies in assessing the activity of sarcoidosis and monitoring the progress of the disease. Resolution of the active disease or clinical control of sarcoidosis by adequate corticosteroid therapy brings the serum angiotensin-converting enzyme level down to the normal range. The test is also helpful during pregnancy when repeated x-ray films of the chest may not be taken. Serum angiotensin-converting enzyme level is a more sensitive index of disease activity than serial chest radiography.

Gallium 67 is a cyclotron-produced radioisotope with a half-life of 78 hours. The isotope accumulates in active sarcoid tissue. Because an abnormal gallium uptake has been described in a wide variety of lung diseases including carcinoma, infections, hypersensitivity pneumonitis, pneumoconiosis and lymphoma, the test is not diagnostically specific for sarcoidosis. However, gallium uptake is a more sensitive indicator of sarcoid activity than serum angiotensin-converting enzyme levels. It also provides an overall picture of pulmonary and extrapulmonary involvement. The test is noninvasive but two factors must be considered before gallium lung scanning is routinely and repeatedly used: cost and radiation dose delivered, particularly in young patients.

Bronchoalveolar lavage is done by placing a fiberoptic bronchoscope in a distal airway and instilling 100 to 150 ml of normal saline in 20- to 30-ml aliquots and recovering the lavage fluid by suction. The immune effector cells in bronchoalveolar lavage fluid in normal nonsmokers consist of more than 90 percent alveolar macrophages, less than 10 percent lymphocytes and less than 1 percent polymorphonuclear leukocytes. In sarcoidosis there is a marked increase in T-lympho-

cytes in the lavage fluid and their numbers reliably reflect the intensity of sarcoid alveolitis. Because the activity of pulmonary sarcoidosis can be correctly judged by analyzing the bronchoalveolar fluid, this technique is extremely useful in staging sarcoidosis patients and monitoring their response to therapy.

Results of serum angiotensin-converting enzyme level, gallium 67 scan and bronchoalveolar lavage lymphocyte count not only correlate with clinical disease activity but also provide better understanding of biochemical and immunologic features of sarcoidosis. It has been suggested that the three markers probably reflect different stages of the granulomatous process. Further studies are needed to clearly define the indications for their routine use.

OM P. SHARMA, MD

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The Clinical Use of Monoclonal Antibodies

In 1975 Kohler and Milstein developed a relatively simple technique for producing large quantities of monoclonal antibody of desired specificity, that is, antibody secreted by a single cell and its clonal progeny, uncontaminated by other antibodies. One of the initial applications of this technology was the use of monoclonal antibodies to distinguish subpopulations of human T-lymphocytes that turn the immune response either on or off. In the peripheral blood of normal persons the proportion of T-cells expressing "helper" or "suppressor" markers is relatively fixed, possibly reflecting an appropriate balance of the functions of these subsets. In a number of disorders, such as multiple sclerosis and acquired immune deficiency syndrome (AIDS), these proportions are altered, and often the alterations correlate with disease activity. In recipients of organ allografts, the ratio of suppressor-to-helper cells may predict graft survival. In patients who have rheumatoid arthritis treated with total lymphoid irradiation, a dramatic increase in the ratio of suppressor-to-helper cells occurs with clinical improvement. Based on observations such as these, the monitoring of lymphocyte subsets with monoclonal antibodies will likely become an increasingly common practice.

The potential uses of monoclonal antibodies extend far beyond analyzing lymphoid cells. Monoclonal antibodies to human leukocyte antigen (HLA) markers such as HLA-B27 have already been produced and may prove useful in disease diagnosis and histocompatibility testing. It should be possible to produce monoclonal antibodies with specificity for any cell type, for use in histopathologic diagnosis or x-ray imaging. Antibodies to infectious agents or tumor-associated antigens can be used for immunodetection in vivo or in vitro.

Perhaps the most exciting of the potential applications of monoclonal antibodies is their use in vivo as therapeutic agents. Their appeal in this regard is due not only to their exquisite specificity for target antigens but also to the fact that antibodies can be attached to other compounds such as drugs, radioactive isotopes or toxins for delivery of those compounds to specific target tissues. Murine monoclonal antibodies to lymphocyte surface antigens have already been used in experimental protocols to treat leukemia and lymphoma, and the results have been encouraging. One limitation of mouse monoclonal antibodies is that they induce the formation of antimouse antibodies in human hosts, and these antiantibodies can neutralize the desired effect of a therapeutic antibody. Although this problem may be obviated by the use of human monoclonal antibodies, therapy with monoclonal antibodies must be limited to experimental settings until optimal protocols are developed. Nonetheless, there is little doubt that this new approach will ultimately contribute significantly to the treatment of a variety of disorders.

EDGAR G. ENGLEMAN, MD

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Streptokinase and Acute Myocardial Infarction

Extensive myocardial necrosis is a frequent cause of chronic heart failure and death in patients who have acute myocardial infarction. Measures designed to limit myocardial necrosis by limiting myocardial oxygen demand, increasing collateral blood flow or correcting various ischemic cellular defects have not proved satisfactory in the clinical setting. The need for restoration of antegrade flow in an occluded coronary artery has become obvious. Revascularization by emergency surgical bypass appears impractical; moreover, its ability to salvage a significant portion of jeopardized myocardium remains uncertain. Based on postmortem studies, in vivo angiography and intraoperative evidence that thrombosis is usually the cause of coronary occlusion in acute myocardial infarction, studies have been undertaken to determine if it is possible to reopen the occluded coronary artery rapidly by direct intracoronary administration of thrombolytic agents like streptokinase, urokinase or streptokinase plasminogen mixture for lysing occlusive clots. These studies have since confirmed that the arteries can—in 70 percent to 90 percent of cases—be reopened, usually within 30 minutes. Because the ruptured atherosclerotic plaque that initially triggered the thrombosis is still present, the artery must be protected by effective anticoagulation for about three months, initially with intravenous administration of heparin and, after five to seven days, warfarin. When the coronary artery was completely occluded and collaterals were not visible on angiography, significant myocardial salvage was usually not

achieved when the coronary artery was reopened later than four hours after occulsion, which is indicated by the onset of pain. Myocardial salvage was assessed by thallium 201 scintigraphy done before and after recanalization. Significant myocardial salvage resulted in a delayed improvement of abnormal regional wall motion and rises in left and right ventricular ejection fractions days and weeks after reperfusion. There is suggestive evidence that successful early reperfusion results in significantly reduced mortality. Hematomas at the site of punctures and arrhythmias, usually not serious, are fairly frequently occurring complications of intracoronary thrombolysis. In recent studies in which streptokinase was administered in large doses intravenously rather than intracoronarily, results were similar to those of the intracoronary route. Large controlled studies will be necessary to definitely assess the effect of thrombolysis on mortality, to identify subsets of patients who can benefit most from the procedure and to define time limits of effective intervention in various patients.

WILLIAM GANZ, MD

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Chemotherapy for Disseminated Germ Cell Cancer

GERM CELL TUMORS arise from the testes and ovary as well as extragonadal sites. Whereas localized germinal neoplasms are curable by surgical treatment or radiotherapy, or both, disseminated tumors such as advanced testicular cancer have historically been difficult to eradicate. Since the mid 1970s, new drugs such as bleomycin and cisplatin have been used in combination chemotherapy programs for patients who have advanced testis cancer. The three-drug combination of vinblastine, bleomycin and cisplatin has been used by Einhorn and co-workers with dramatic results. In an initial series of 47 patients who had advanced testis cancer, 33 (70 percent) achieved complete disease regression using four cycles of the three-drug combination administered over a 12-week induction therapy period. Similar regression rates have been achieved in subsequent series. Complete response correlated with the bulk of the initial tumor—large tumor masses being unfavorable for achieving complete regression—but all histologic subtypes of germ cell tumors responded.

In 4.5 to 6.5 years of follow-up, 6 out of 33 originally complete responders have relapsed. Most relapses occurred in the first year, none after two years. Patients in continuous complete remission at two years are considered cured. During the initial development of "Einhorn" chemotherapy, maintenance chemotherapy was administered for two years. Recent studies have shown no benefit from this type of prolonged maintenance treatment. Among large series of testis cancer patients achieving complete remission with combination chemotherapy, the relapse rate even without maintenance treatment may be as low as 10 percent or less.

Germ cell neoplasms are diseases of young people. New chemotherapy combinations have markedly increased the curability of germ cell tumors of the testes and appear to be very beneficial in the treatment of ovarian germinal neoplasms and extragonadal germ tumors as well.

MARK R. GREEN, MD

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Hepatitis B Vaccine

A VACCINE (Heptavax-B, Merck, Sharp and Dohme Research Laboratories) has been introduced that offers the potential of eliminating viral hepatitis, type B. The disabling effects of acute type B hepatitis, combined with the long-term features of chronic viral infection that include the possible development of hepatoma, make this an extremely important breakthrough. Considerations of cost, availability and safety, however, combined with a population at relatively low risk, have already produced controversy about whom to vaccinate.

The development of this vaccine has taken advantage of two characteristics of the hepatitis B virus: the chronic carrier state and the overproduction by the carrier of coat protein (hepatitis B surface antigen). The antigenic particle is much smaller than the virus itself and is separated by ultracentrifugation. Further steps including formalin inactivation lead to a highly purified, theoretically safe product. Because we are unable to grow this virus in culture, plasma from chronic carriers is used. Future research or the use of modalities such as recombinant techniques may of course change this approach.

The antigen in this vaccine achieves its purpose. In more than 90 percent of recipients in studies to date, antibody titers develop. That this antibody is protective has been shown in studies with homosexual men who have an extraordinary attack rate that is nearly eliminated in vaccine responders. Whether or not this protection is retained for a long time, as expected, will need to be shown.

Safety is an issue that cannot be adequately addressed at this time. No major side effects have been reported to date in trials totaling 25,000 to 50,000 doses of vaccine. What will happen when this number reaches the millions is pure conjecture. All of the various concerns about vaccines have been voiced. But an extremely careful development and testing program has provided as much information as we can expect at this time.

Based on efficacy, presumed safety and cost (about $100 per treatment) what can we recommend? Clearly those at greatly increased risk such as promiscuous homosexual men (80 percent risk) and sexual partners of carriers (50 percent risk) need attention. Health care workers in direct contact with blood, either in patient care (dialysis workers, special unit nurses and the like) or ancillary services (such as phlebotomists and clinical laboratory technicians) have a variable

exposure with an estimated risk of 2 percent to 3 percent a year. In the view of most experts, this amount of risk justifies immunization.

The manufacturer recommends antibody testing (hepatitis B surface antibody at $20 per test) before vaccination to eliminate unnecessary and costly injections in people who have naturally acquired immunity. While this is the current standard, its cost effectiveness has been questioned. Clearly the response rate to the vaccine eliminates the need for follow-up antibody studies in all but special circumstances.

What is needed is a low-cost safe method for attacking this global problem. We now have what appears to be a very good beginning.

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Plasmapheresis as Therapy

PLASMAPHERESIS, or plasma exchange, a new and sophisticated form of bloodletting, is rapidly becoming a major therapeutic tool for the treatment of a variety of disease processes. This innovation has been made possible by technologic advances in centrifugation that allow the separation of various cell components from plasma of human blood. About 41,000 such apheresis procedures were done in the United States last year on a minimum of 41 different disease processes. The data base for the entire industry is based on anecdotal reports. Only now are double-blind studies being done to further delineate the indications and to compare the efficacy of this form of treatment with other conservative measures. The one group of diseases wherein the use of plasmapheresis seems to be clearly accepted by all is the hyperviscosity syndromes in which aberrations in blood flow occur as a result of the presence of abnormal blood proteins. Here the procedure is of most value in an acute crisis. Long-term management requires both plasmapheresis and immunosuppressive therapy.

Despite the limited data base, recognized authorities in the field suggest that there is enough information available to justify plasmapheresis in certain clinical settings. In most cases it is assumed that immunologic mediators of disease are removed in the process of plasmapheresis. Besides the hyperviscosity syndromes, plasmapheresis may also be beneficial for the following disorders:

- Myasthenia gravis, especially in patients who have failed to respond to steroids and antimetabolite therapy or in those who are in an acute respiratory crisis.
- Goodpasture's syndrome, biopsy proved or associated with lung hemorrhage, and acute crescentic nephritis that is rapidly progressing and not responding to steroid drugs.
- Lupus nephritis, the classic circulating immune complex disorder. Unfortunately, the criteria for the use of plasmapheresis have not yet evolved in this disorder and double-blind studies are only now under way to exactly define its value.
- Rapidly progressing systemic sclerosis with not only skin but also multiorgan system involvement, though the number of cases so far is extremely small and widespread clinical use probably cannot be justified and should be restricted to academic centers. The same holds true for other rheumatic diseases such as polymyositis and dermatomyositis.

Plasmapheresis is a popular and rapidly expanding area in which only time and additional studies are needed to give this tool its proper place in clinical practice. English physicians have recently suggested that all patients who receive an apheresis procedure should be in a clinical registry so that a maximum amount of information can be obtained regarding this treatment. This should also be done in this country.

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Calcium Channel Blocking Agents in Cardiovascular Medicine

THE CALCIUM CHANNEL blocking agents are a heterogeneous group of compounds that represent a new generation of drugs for the treatment of cardiovascular disease. Their therapeutic actions derive from their capacity to inhibit calcium flux through the "slow" channels of cardiac and smooth muscle cell membranes. The slow channels are so named because cellular entry of calcium is normally delayed during electrical depolarization until the plateau phase of the action potential, in contrast to sodium transmembrane passage through the "fast" channels at the initiation of depolarization. The electrical and contractile functions of cardiac and smooth muscle tissue are dependent on this phasic cellular entry of calcium which activates calcium-dependent adenosine triphosphatase (ATPase), an essential step in excitation-contraction coupling. Skeletal muscle cells, however, have abundant intracellular calcium stores and their activity does not depend on influx of calcium. Therefore, agents that inhibit calcium flux can modulate cardiac and smooth muscle activity, an effect with therapeutic potential in certain conditions.

The cardiovascular effects of the calcium antagonists are the result of their direct and indirect actions on the heart and vasculature at multiple levels. The direct effects of inhibition of calcium transport by these agents are smooth muscle relaxation and thus systemic and coronary vasodilation and negative cardiac inotropy. Depending on the specific drug, these agents either have

negligible actions on cardiac electrophysiologic function or prolong the refractory period of the atrioventricular node and reduce sinoatrial node automaticity. These effects result in reduction of blood pressure, prevention of coronary vasospasm and antiarrhythmic activity in supraventricular tachyarrhythmias. The coronary vasodilating action provides an important mechanism of therapy for coronary vasospastic (Prinzmetal) angina, and lowered blood pressure and negative inotropy favor reduction of myocardial oxygen demand and alleviation of nonvasospastic angina. Reflex sinus tachycardia may occur as a result of vasodilator-induced fall in blood pressure. The modest negative inotropic action may be offset by a reduction of afterload through systemic arterial dilatation, but this is unpredictable. The major adverse effects of the calcium antagonists are extensions of their pharmacologic actions: hypotension, myocardial depression and atrioventricular block.

Three calcium antagonists—verapamil, nifedipine and diltiazem are now available in this country and therapeutic trials have been initiated with more recently developed drugs of this class. All three available agents are vasodilators, though nifedipine is most potent in this regard, and reflex tachycardia due to blood pressure reduction may be significant with this agent. Verapamil and, to a lesser degree, diltiazem produce the inhibitory cardiac electrophysiologic effects enumerated above and nifedipine is devoid of significant, direct cardiac electrophysiologic effects. The Food and Drug Administration (FDA)-approved indications for the use of these agents include coronary vasospastic angina and nonvasospastic angina for all three and, for intravenous verapamil, paroxysmal supraventricular tachyarrhythmias. The calcium blockers have been highly effective in anginal states, alone or in combination with nitrates or β-blockers (or both), in patients in whom the latter drugs have been unsuccessful. These agents are usually used in patients refractory to conventional therapy and can be administered in combination with either nitrates or β-blockers for nonvasospastic angina and with nitrates for vasospastic angina. Although such a combined approach has considerable therapeutic potential, myocardial depression and hypotension are important risks.

Intravenous verapamil has become a first-line agent for the treatment of supraventricular tachyarrhythmias. Current reports indicate that the drug promptly converts paroxysmal supraventricular tachycardia to sinus rhythm in more than 80 percent of patients. Conversion of atrial fibrillation and flutter to sinus rhythm by verapamil administration occurs only occasionally, but in these arrhythmias the drug slows ventricular rate in most patients. Because of its efficacy, intravenous verapamil has had a major impact on the emergency treatment of supraventricular tachyarrhythmias.

The calcium antagonists are associated with side effects in about 10 percent to 15 percent of patients, which can often be managed by decreasing the dosage. Hypotension is the adverse effect of primary concern with intravenous verapamil, which is contraindicated in cases of tachyarrhythmia associated with sinus node dysfunction. Further information is required regarding the clinical pharmacology of these drugs, particularly in relation to drug interactions. In this regard, both nifedipine and verapamil have been reported to raise serum digoxin levels in patients receiving the glycoside.

Current interest in the therapeutic potential of the calcium antagonists, based on their pharmacologic properties, extends to a wide spectrum of cardiovascular conditions. These include hypertrophic obstructive cardiomyopathy, hypertension, congestive heart failure, vasospastic disorders, limitation of myocardial infarct size and myocardial preservation during cardiac operations. The calcium antagonists have already established an important place in the treatment of cardiac disease and their full therapeutic potential has not yet been fully realized.

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Percutaneous Transluminal Coronary Angioplasty

PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY (PTCA) is a promising new catheter technique for dilating stenosed coronary arteries with consequent improvement in coronary blood flow and clinical manifestations of myocardial ischemia. Dotter and Judkins first described a similar method for transluminal recanalization of peripheral arterial stenoses in 1964; hemorrhagic and thrombotic complications limited its use, however. In 1973 Grüntzig developed a double-lumen balloon catheter that was first tested in laboratory animals and then applied sequentially in humans to peripheral and renal arteries, cadaver hearts and coronary arteries during aortocoronary bypass surgical procedures. In September 1977 in Zurich the technique was first used during cardiac catheterization. Since then, it has been used increasingly throughout the world in patients with symptomatic coronary atherosclerosis; its proper role and limits in the treatment of this disease remain a focus of intense clinical investigation.

Initially, only those patients who had single-vessel involvement and a lesion that was proximal, discrete, concentric and noncalcified were selected for the procedure. Cardiologists are now beginning to apply the technique to patients who have multivessel disease where all or most lesions appear amenable to dilatation. Lesions situated in or at the anastomosis of a saphenous vein graft have also been dilated successfully. All patients should be candidates for bypass graft operation because in 6 percent to 8 percent of percutaneous transluminal coronary angioplasty procedures a sudden occlusion or deterioration of flow causes impending infarction and immediate surgical intervention is then necessary.

Patients undergoing percutaneous transluminal coronary angioplasty generally are treated before, during and after the procedure with administration of aspirin, dipyridamole, nitrates and a calcium blocker (for example, nifedipine) to inhibit thrombus formation and spasm at the site of the dilatation. Low-molecular-weight dextran and heparin also thwart thrombotic occlusion during and immediately after the procedure.

In appropriately selected cases, the primary success rate (at least a 20 percent improvement in the degree of stenosis) is achieved in 60 percent to 85 percent of patients treated. Lesions in the left anterior descending coronary artery appear to be most amenable to a successful primary result. Myocardial infarction by either electrocardiographic or enzymatic criteria has been noted in about 3 percent of patients, and hospital death has occurred in 1 percent or less of cases reported on in most published series. Other complications, including ventricular arrhythmias, bradycardia, hypotension and femoral or brachial artery occlusion, are similar in frequency to their incidence with routine cardiac catheterization and angiography.

In the first 6 to 18 months after percutaneous transluminal coronary angioplasty, about 80 percent of successfully treated patients continue to be free of symptoms. However, follow-up angiography of both symptom-free and symptomatic patients shows a restenosis rate (at the site of angioplasty) of about 30 percent.

This procedure is also being applied in concert with intracoronary infusion of streptokinase for the treatment of acute myocardial infarction. This application is strictly experimental and should not be considered a standard form of therapy at the community level. In fact, continuation of careful follow-up studies will be necessary before percutaneous transluminal coronary angioplasty can be granted a permanent role in the treatment of the clinical syndromes associated with coronary atherosclerosis.

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Toxic Shock Syndrome

TOXIC SHOCK SYNDROME is an acute febrile illness involving multiple organ systems and associated with hypotension and rash. Patients who have toxic shock syndrome are often found to carry or to be infected with *Staphylococcus aureus* bacterium. Typically the syndrome occurs in young, previously healthy, menstruating women who use tampons. It is characterized by the following clinical presentation: fever (temperature 38.9°C [102°F] or higher); syncope, hypotension or shock; vomiting and watery diarrhea; diffuse inflammation of the mucous membranes; diffuse erythroderma or petechial skin rash; desquamation of the hands and feet during the convalescent period, and laboratory evidence of multiple organ dysfunction.

Of the reported cases of toxic shock syndrome, 92 percent are associated with menstruation, with 99 percent of those cases occurring in tampon users. Menstrual toxic shock syndrome cases occur predominantly in whites (98 percent), with a mean age of 22 years. The case-fatality ratio with menstrual toxic shock syndrome is 3.5 percent. There is an increased risk of menstrual toxic shock syndrome developing with the use of superabsorbent tampons. Although the vast majority of cases have occurred in menstruating women, it is being reported with increasing frequency in men and in children of both sexes. The mean age for nonmenstrual toxic shock syndrome is 27 years, with a 9 percent case-fatality ratio. *S aureus* isolated from nonmenstrual cases is similar in all respects to the *S aureus* isolated from patients who have the menstrual syndrome.

Intravascular invasion of *S aureus* is less important than the production, absorption and action of *S aureus* toxins. Pyrogenic exotoxin C and enterotoxin F are low-molecular-weight glycoproteins found in 90 percent of *S aureus* strains isolated from patients who have toxic shock syndrome. The toxin-producing strain of *S aureus* is found infrequently in patients who do not have the syndrome. Because the toxin-producing strain of *S aureus* fails to elaborate large amounts of hemolysin, lipase and nuclease, it may evade normal defenses by not invading tissue and thus not inducing a local inflammatory response. High antibody titers to enterotoxin F are found in 80 percent of the normal adult population, whereas low or no antibody titers to enterotoxin F are found in 95 percent of patients in whom toxic shock syndrome develops.

Characteristic pathologic findings in the vaginal-cervical mucosa are mucosal separation beneath the basal layer with ulceration, severe vasodilatation, inflammation and thrombosis but minimal bacterial invasion. The primary pulmonary findings are severe capillary congestion, intraalveolar hemorrhage, atelectasis and hyaline membrane formation. Periportal inflammation with microvesicular fatty changes and centrilobular congestion are observed in the liver. Pathologic findings in the kidney are typical of acute tubular necrosis.

Commonly observed sequelae of toxic shock syndrome are the late-onset rash, reversible patchy alopecia, telogen effluvium, prolonged weakness, fatigue and exercise intolerance. A third of patients will have recurrence of the syndrome at least once. Less commonly, persistent headache, confusion, memory loss, inability to compute and loss of higher integrative functions have been observed.

Treatment of toxic shock syndrome includes vigorimmediate removal of the tampon if present. Antious fluid resuscitation with crystalloid solution and microbial therapy with β-lactamase-resistant antistaphylococcal antibiotics during the acute illness is effective in reducing the rate of recurrence. Whether or not

antimicrobial therapy shortens the acute episode of toxic shock syndrome is uncertain. Discontinuation of tampon use following the initial episode also reduces the rate of recurrence of the syndrome and is independent of the antibiotic effect. Occasionally other specific therapy is required to correct hypocalcemia, acid-base imbalance, adult respiratory distress syndrome, acute renal failure, myocardial dysfunction and disseminated intravascular coagulation with thrombocytopenia.

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Indications for Digoxin Therapy for Congestive Heart Failure

ALTHOUGH HENRY CHRISTIAN in 1919 showed the usefulness of digitalis for reducing congestive heart failure in patients who have a regular rhythm, several studies have questioned the efficacy of digoxin in treating patients who have chronic congestive heart failure with sinus rhythm. Three recent investigations provide information from which guidelines can be set for selecting patients for digoxin therapy.

Arnold and co-workers measured resting and exercise hemodynamic parameters in nine patients who had chronic congestive heart failure in sinus rhythm. All patients had an S_3 gallop and cardiomegaly and had had at least one prior episode of pulmonary edema. After withdrawal of digoxin, a significant reduction in the cardiac index (13 percent at rest, 11 percent with exercise) and a rise in pulmonary capillary wedge pressure (38 percent at rest and 27 percent with exercise) were noted. Five of the nine patients also had symptomatic deterioration with digoxin withdrawal. Immediate readministration of digoxin restored left ventricular function to that obtained after long-term therapy.

Lee and associates randomly selected 25 patients (mean age 61) who had had a prior episode of congestive heart failure who were on digoxin therapy (serum concentration 1.2 ng per ml) in a double-blind, crossover protocol. Of 25 patients 22 received diuretics. Using a scoring system based on dyspnea, rales, heart rate, jugular venous distention and findings on chest roentgenogram, 14 of 25 patients showed improvement with digoxin therapy. Multivariate analysis showed that the S_3 gallop correlated best with response to digoxin. The average ejection fraction during the placebo period of those patients who responded was .19, compared with .42 for the nonresponders.

Fleg and colleagues randomly selected in a double-blind, crossover fashion 30 patients (mean age 69) who had had an episode of congestive heart failure. In contrast to the study of Lee and co-workers, only one of their patients had an S_3 gallop. Of 30 patients 23 were receiving diuretics. No exacerbation of congestive heart failure that could be attributed to digoxin withdrawal was noted in a follow-up period of 19 months.

Because digoxin is the seventh most commonly prescribed drug in the United States and the incidence of digoxin toxicity may be as high as 25 percent, it is extremely important to clearly define the indications for digoxin therapy. The only absolute contraindication to the use of digoxin is digoxin toxicity. Relative contraindications are idiopathic hypertrophic subaortic stenosis (with increased outflow obstruction when contractility is increased by digoxin), congestive heart failure due to limitation of ventricular filling (for example, constrictive pericarditis or mitral stenosis with sinus rhythm) and conduction system disease (cardiac amyloidosis, bradyarrhythmias and anomalous atrioventricular conduction such as in the Wolff-Parkinson-White syndrome). Care must always be taken when using digoxin in patients who have conditions with increased risk of digoxin toxicity, such as hypokalemia, hypoxia, hypercalcemia, myxedema, multifocal atrial tachycardia, renal failure and in combination with drugs (such as quinidine) that influence digoxin metabolism.

Digoxin is of clear benefit in cases of supraventricular tachyarrhythmia such as atrial fibrillation and atrial flutter. Its usefulness in patients who have paroxysmal supraventricular tachycardia may be supplanted by calcium-entry blockers. For patients in sinus rhythm digoxin is of benefit when congestive heart failure is due to dilated states (as with ischemic heart disease or hypertensive cardiomyopathy), valvular heart disease excluding mitral stenosis and congenital heart disease. For volume overload states (as with mitral or aortic regurgitation), digoxin and especially peripheral vasodilators are useful. In Fleg's study no patients deteriorated when digoxin was withdrawn and in Lee's study 56 percent of patients showed improvement with digoxin therapy. Therefore, a significant fraction of patients in sinus rhythm who have chronic congestive heart failure can be managed with diuretics alone. A management strategy would be to first treat such patients with limitation of physical activity, salt restriction and diuretics. If the congestive heart failure only partially resolves or if a patient has an S_3 gallop and a low ejection fraction, a trial of digoxin is then warranted.

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Third-Generation Cephalosporins

THE THIRD-GENERATION CEPHALOSPORINS are a group of drugs (cefotaxime, moxalactam, ceftizoxime, ceftriaxone, cefoperazone, ceftazidime and so forth) in which biochemical manipulation of the side chains attached to the basic β-lactam structure inhibits hydrolysis by β-lactamases. As a result of this protection, these drugs have more activity particularly against Gram-negative enteric bacteria than earlier cephalosporins, while maintaining the same relative safety. Among them-

selves, the newer cephalosporins vary in activity against individual bacteria and in pharmacokinetics.

Cefotaxime, moxalactam and cefoperazone are the only third-generation cephalosporins licensed in the United States but others, such as ceftazidime, should soon follow.

Most third-generation cephalosporins have excellent activity in vitro against strains of *Escherichia coli, Klebsiella, Proteus, Providencia, Morganella* and *Citrobacter*. Normal peak serum concentrations of these drugs exceed by 100 times the minimal inhibitory concentration of the microorganisms. Third-generation cephalosporins also have excellent activity against the β-lactamase-producing strains of *Haemophilus* and *Neisseria* species and against anaerobes. Activity against *Pseudomonas aeruginosa* varies; their value depends on comparative testing with extended-spectrum penicillins and aminoglycosides. Activity against *Staphylococcus aureus* is significantly less than that of cefazolin and, because activity against *Streptococcus pyogenes* and *Streptococcus pneumoniae* is also less than the penicillins, the third-generation cephalosporins offer no advantage in treatment against these Gram-positive species. These drugs have no activity against group D streptococci (enterococci) and *Listeria*.

Adverse side effects are infrequent and are similar to those with other cephalosporins: namely, rash, diarrhea, *Candida* vaginitis, instances of granulocytopenia and thrombocytopenia and transient elevations in hepatic enzyme levels. Prolongation of the prothrombin time, which is correctable with vitamin K administration, has been observed with moxalactam. Superinfection with multiresistant organisms is a potentially important complication as these drugs may promote the prevalence of resistant bacteria.

In clinical trials the third-generation cephalosporins have been effective in treating respiratory tract, urinary tract, abdominal and gynecologic infections and meningitis due to Gram-negative enteric bacteria. However, except for cases of Gram-negative meningitis, in which treatment with moxalactam or cefotaxime has dramatically increased the success rate, clinical studies comparing third-generation cephalosporins with conventional antimicrobial therapy have shown only equivalency. These remarkable and expensive new drugs thus provide an additional means of therapy of potential but unproved superiority to present regimens.

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Periodic Health Examinations

PERIODIC HEALTH EXAMINATIONS are an American institution. Their earliest roots can be traced to successful public health programs aimed at controlling such diseases as typhoid, tuberculosis and smallpox. The basic principles that stimulated the growth and acceptance of this movement are simple and seductive: that periodic examinations can detect diseases in asymptomatic persons in an early stage and that prompt treatment will lead to diminished morbidity and mortality. Early uncontrolled studies showed impressive health gains. The American Medical Association formally endorsed the annual examination in 1922 and prepared a manual detailing the methods of providing this service. Over the next 50 years, comprehensive periodic health examinations became the standard of care and a symbol of the best in American medicine. While epidemiologists identified risk factors for such major health problems as coronary artery disease, early detection programs for cervical, colon and breast cancer showed promising results and biomedical engineers provided automated multiphasic testing. Increasing public demands fostered by a profitable health industry led to the use of more and more untested screening procedures.

In spite of this popular support, critics of routine periodic screening have recently begun to question the purpose, content, frequency, yield and cost of such examinations. At the same time, government and other third-party insurers and health maintenance organizations are insisting on closer evaluation of efficacy and cost effectiveness of many health care practices. Results of a number of ambitious studies of periodic health screening have recently been published. Although each reaches somewhat different conclusions, they are similar in their attempt to place the periodic health examination on a sound, scientific foundation.

The most comprehensive of these studies was published in 1979 by the Canadian Task Force on the Periodic Health Examination. An expert, 11-member panel supported by an international group of consultants spent more than three years reviewing the world medical literature on 78 potentially preventable conditions. To ascertain whether early detection would be beneficial, available information on the burden of suffering, the characteristics of the early detection procedure and the effectiveness of preventive measures or treatment modalities was carefully evaluated. The task force incorporated their conclusions into a lifetime program of 18 health protection packages. For example, at specified intervals for all adults, measurement of blood pressure, examination of oral cavity, evaluation of hearing, stool screening for occult blood, immunization against tetanus, counseling against smoking and alcoholism and advocacy of the use of seat belts were recommended. For adult women, periodic contraceptive counseling, physician breast examination and a Papanicolaou's test were added. Yearly mammography was suggested for women between 50 and 60. For adults older than 65 years, periodic assessment of physical, social and psychologic function and yearly influenza immunization were recommended. The task force failed to find sufficient evidence to justify routinely doing a "complete" history and physical, blood count, chemistries, analysis of urine, electrocardiography and chest x-ray.

It should be emphasized that the recommendations of the task force and those of the other three recent

studies are for preventive measures on behalf of apparently well, asymptomatic persons at low medical risk. They are not intended for those persons at increased risk of a condition or who have symptoms. There remains a great deal to be learned about the efficacy of periodic health examinations. Well-designed studies to assess the usefulness of health screening procedures still remain to be done. Accepting that many of these recommendations are based on incomplete data, primary care practitioners should select a periodic screening measure consistent with their interpretation of available information and incorporate it into a specific plan of preventive care for each patient.

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Acquired Immune Deficiency Syndrome (AIDS)

ACQUIRED IMMUNE DEFICIENCY SYNDROME (AIDS) is the term currently applied to an expanding epidemic of severe immunosuppression first recognized as an increased occurrence of Kaposi's sarcoma and *Pneumocystis carinii* pneumonia among previously healthy persons. Between June 1, 1981, and February 10, 1983, the Centers for Disease Control (CDC) received reports of 1,051 cases of acquired immune deficiency syndrome (that is, Kaposi's sarcoma or serious opportunistic infections) with fatality in 41 percent overall and in greater than 60 percent in those diagnosed more than a year ago. Although 80 percent of the reported cases were concentrated in six cities, predominantly on the East and West Coasts, well-documented cases have occurred in more than 33 states and 13 foreign countries. The reported incidence continues to rise rapidly.

Populations considered to be at risk include homosexual or bisexual men (75 percent of cases), heterosexual male and female intravenous drug abusers (13 percent), heterosexual Haitians with no history of intravenous drug abuse (6 percent) and persons with hemophilia A (three cases). Although the CDC's definition of acquired immune deficiency syndrome requires the unexplained occurrence of Kaposi's sarcoma, *P carinii* pneumonia or infections associated with defective cell-mediated immunity, the full spectrum of the syndrome may include asymptomatic abnormality of lymphocytes now reported in gay men and nonspecific constitutional symptoms with or without generalized lymphadenopathy. The prevalence of other malignant disorders (diffuse undifferentiated non-Hodgkin's lymphoma, squamous carcinoma of the anorectum and of the oral cavity) and autoimmune thrombocytopenia also appears to be increased in gay men.

The pathogenesis of acquired immune deficiency syndrome is unknown. Epidemiologic evidence is most consistent with the presence of an agent or agents transmissible by blood. Two immunosuppressive and oncogenic herpesviruses, cytomegalovirus and Epstein-Barr virus, are candidate agents, but genetic (HLA-DR5) factors and amyl nitrite exposure have also been implicated.

There is no laboratory screening test for acquired immune deficiency syndrome. Immunologic abnormalities in established cases have included lymphopenia, cutaneous anergy and alterations in T-lymphocyte subsets as measured by monoclonal antibodies to markers for suppressor and helper function. However, delayed cutaneous hypersensitivity and quantitatively normal lymphocyte counts do not exclude a significant defect in immunoregulation and abnormalities in T-cell subsets are not yet established as predictive of the development of this disorder.

Physicians should be familiar with the features of this syndrome and keep patients in identified risk groups under surveillance. Gay men who wish to reduce their risk should reduce the number of sexual partners.

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Editorials

Political Philosophies and Some Realities in Health Care

HEALTH CARE is emerging as an important arena for the testing of political philosophies in the real world. A major reason for this phenomenon is the unprecedented social, economic and technologic interdependence that has developed in the field. The present-day stereotypes of liberal and conservative political philosophy, however, both seem somehow to miss the mark when it comes to the realities of health care. At the risk of oversimplification it can be said that each is rooted in a fundamental tenet of American belief: Liberalism has a basis in the belief that all men are created equal—which has led to increasing manifestations of egalitarianism, such as anti-intellectualism and antiprofessionalism. Conservatism is rooted in the belief that, by dint of hard work and a little luck, one can advance in this world and is then entitled to its rewards—that is, one is entitled to have what one can pay for. This necessarily leads to elitism expressed in various ways. These beliefs appear to be in fundamental conflict and this has become readily apparent in the field of health care where elitism (professionalism) and egalitarianism (antiprofessionalism) are often at odds.

These two political philosophies are joined in the issues of quality, access, costs and control of health care. The one calls for equal access to high quality health care for all, and the other for different levels of care depending upon who can afford what. It is likely that costs of care will defy the approach of either political philosophy. The one has already driven the costs beyond the acceptable reach of society, and the other will never be able to deny care to those who really cannot afford it. And the one would centralize control of health care by nationalizing it under federal regulation, but this would not work because centralized regulation has already been shown unable to keep pace with the rapid changes that occur in health care. And the other would deregulate the health care system, but in the process of doing this is finding it necessary to place restrictions hampering and sometimes even destroying the internal controls that have been developed in the private sector to bring some kind of order into a dynamic and ever-changing system with many essential yet interdependent parts.

It is clear that issues of access, quality, cost and control are not likely to be resolved simply by applying either stereotyped political philosophy. Health care is not an abstract concept that can be dealt with by abstract philosophical approaches. Health care is a reality that touches the lives and well-being of people. It is likely that it is the political philosophies that are unreal when it comes to health care and this may be because neither of the stereotypes addresses the reality of the conflict of fundamental beliefs that is coming into focus around issues in health care.

It would seem that both these major political philosophies will need to find a genuine accommodation in health care. The realities of human needs which are very personal, costs which are less personal, and the nature of a highly specialized and technologic, social, economic and politically interdependent health care system which is relatively impersonal, require that an accommodation be sought. Perhaps it is time to return the problem to the people, to return the responsibility for collaboration and for the control of health care to local communities or regions. It could be valuable to allow the decisions about access, quality, costs and controls to be made by those who need health care and those who can provide it—where fundamental beliefs that may be in conflict can be accommodated to the real problems at hand.

—MSMW

Advances in Obstetrical Technology

A NUMBER OF IMPORTANT ADVANCES have occurred in obstetrics in the past few decades, but the most dramatic must surely be those concerned with the detection of a fetus in difficulties.

The potential hazards that can now be detected fall broadly into two categories: (1) in utero inadequate growth and asphyxia and (2) structural, biochemical or physiologic defects. Over the years a number of clinical and laboratory methods have been proposed as techniques of fetal surveillance. There was a period when the multiplicity of tests created a good deal of confusion—particularly in the former category—but the situation is now stabilizing, though many of the proposed tests have been discarded. The authors of the Medical Progress article in this issue highlight three approaches that are emerging as the most effective in detecting a fetus with problems: amniocentesis, beat-to-beat fetal heart rate monitoring and ultrasound imaging.

The emphasis placed on these sophisticated methods should not be taken to indicate that the cheaper clinical screening approaches have no value. For example, the prime means of screening for and detecting most growth-retarded fetuses remain serial measurements of fundal height with a tape measure. This has been shown to be effective in detecting up to 80 percent of growth-retarded fetuses if there is inadequate fundal growth during a three- to four-week period in the third trimester.[1]

Some researchers have proposed screening the entire population with either hormonal measurements (for example, maternal estriol or human placental lactogen) or ultrasound measurements. This has not gained widespread acceptance, primarily because the procedures do

not fit the criteria for screening tests, such as low cost, lack of false-negative results and ease of performance.

The use of "high risk" categorization in both the antepartum and intrapartum periods is still a valuable aid in signifying those pregnancies in need of more attention and further testing by more specific methods. A defect with this screen, however, has become obvious in recent years, in that even a low-risk woman may have an adverse reproductive outcome.[2] Two major categories in such patients are antepartum stillbirth and asphyxial morbidity during labor. A possible screen for antepartum stillbirth is fetal movement counting, which is now widely accepted in Britain and elsewhere, but which has been struggling to gain respectability in North America. The publication of extensive clinical trials of its efficacy should ensure its acceptance and usage.[3]

Antepartum fetal heart rate monitoring has been proposed as a screen in all patients, but this has not been widely accepted. The major reasons include cost, difficulty of timing in relation to the morbid event and proof that its benefit will outweigh the risks. The major risk includes high false-positive rates, that is, a large number of fetuses with "abnormal" results by current criteria are in fact quite normal. Such false-positives may precipitate unnecessary intervention. The addition of other observations, such as fetal movement, may help to diminish the problem.

Intrapartum fetal heart rate monitoring is still plagued by inappropriate interpretation in some hands, despite a growing understanding through experimental studies of the physiologic meaning of various aspects of fetal heart rate patterns during asphyxia. More facts are needed, however, regarding the origin and significance of fetal heart rate variability and its relationship to cerebral and myocardial oxygenation. Also, continued education of an obstetric team is required to keep all up to date with recent progress. Despite its drawbacks, fetal heart rate monitoring is likely to remain the prime screen for intrapartum asphyxia for decades to come.

Ultrasound imaging is widely used for gestational age dating, but a rarely mentioned defect is the variance of the measurement in clinical usage. This is most likely due to the absence of uniformity of criteria, variation in populations and relative lack of expertise. Most published reports are by skilled investigators from research institutions, and this gives an unnecessarily optimistic view of its accuracy. In clinical usage, gestational age can at best be determined to within about two weeks at any stage of gestation. The variation imposes grave difficulties in accurately detecting changes in cases of suspected growth retardation. As with fetal heart rate monitoring, however, improvements can be expected by such approaches as better education and improved criteria.

Several conclusions emerge from a consideration of the newer technology in obstetrics: (1) A careful clinical history and examination are still important, (2) cheap clinical screening techniques remain the basis of good obstetrical practice and (3) the sophisticated tests potentially abound with "false abnormal positives," and require knowledgeable interpretation in light of the whole clinical case.

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A Mantle of Leadership

IT SEEMS THAT circumstances beyond its control have unexpectedly thrust a mantle of leadership upon the shoulders of the California Medical Association (CMA). A revolution in the way medicine is practiced has begun in California as a result of the so-called contracting legislation which was hurriedly enacted by the California legislature and signed by the governor in the summer of 1982, without any of the customary public hearings or any chance for comment by patients, physicians or others who might be affected by it. As a result, new and untested practice arrangements are coming into being. The nation is watching what happens in California and the nation's physicians are watching to see how well the CMA wears this mantle of leadership which it neither sought nor wanted.

A sharp interaction of social, economic and political forces is occuring. The long-standing social goal of equal access to needed health care of good quality continue to be supported by the medical profession and many others, but the cost of this is being seriously challenged by government and others who have been paying the bills. The currently ascendant economic theory contends that health care costs can be contained if the economic forces of the free market can be brought into play. In a word this means competition. Rulings by the United States Supreme Court and the Federal Trade Commission, as well as a number of federal antitrust actions, have already given substantial endorsement to this approach. And in the summer of 1982 the California legislature, confronted by a fiscal crisis in health care, decided to mandate competition. As someone has put it, the laws that were passed make it possible for doctors and patients to be bought and sold like commodities at discounts and to the lowest bidders. Contracts and contracting for health care are now the order of the day in California. No one knows whether the economic theory is correct, whether mandating competition (for California's Title XIX program, known as Medi-Cal) and making it permissible for other programs in the private sector, will work. And no one knows what effect all this will have on the social and

professional goal of equal access or on quality of care for patients.

Doctors, their patients and the ways of traditional medical practice find themselves caught up in a whirlwind of poorly understood changes. The whole idea of contracting for health care is unfamiliar to many. Federal Trade Commission rulings, antitrust laws and even the labor laws seem almost to conspire to prevent individual physicians or groups of physicians from acting effectively in contract negotiations with more powerful groups for their services. The world of PPO's (preferred provider organizations), EPO's (exclusive provider organizations) and the new forms of corporate practice of medicine is unfamiliar and scary. And in addition, problems of perceived or real conflict of interest among medicine's leaders have already arisen.

But one can honestly report that the California Medical Association is rising to the occasion. In the true tradition of physicians everywhere it is emerging as a principal spokesman for patients and the public, for access for all to needed care, for quality of care in whatever economic circumstances it is rendered, and for the central role of physician and patient in all of health care. It is committed to working within the law —all the laws both new and old, and there are many of them. It has already sponsored a "clean-up bill" to improve the contracting laws. The bill was enacted into law. It is planning for other bills to be introduced into the California legislature. The CMA is collecting data on the contracting activities that are now occurring, both within the framework of the law and outside of it. A contracting handbook has been developed for distribution to physicians. The CMA House of Delegates has authorized the creation of a "brokerage corporation" to serve as a resource for physicians contemplating contracting with PPO's or EPO's or other similar arrangements, in a fashion that does not violate antitrust or other laws. If the federal conditions are acceptable to it, the CMA will seek to become the California Peer Review Organization (PRO) and in this way help to assure that the quality of patient care is maintained in the various contracting arrangements in which doctors and patients may find themselves. And in yet another dimension it has risen to the occasion and will soon address the issues of real or perceived conflicts of interest among its own professional leaders who may also have a financial or other interest in one of the new legalized competitive (for profit) arrangements for delivering health care. A number of other innovative proposals are under study and some no doubt will be implemented.

Physicians in California and elsewhere in the nation may be confident that the CMA has accepted this unwanted mantle of leadership and is working diligently to protect patients, the quality of patient care and the working relationships of physicians and patients in what has to be the beginning of a new era in the delivery of health care in this nation.

—MSMW

Infection Prophylaxis in Neutropenic Patients—A Controversial Subject

DESPITE THE INTRODUCTION of many effective broad-spectrum antibiotic agents during the past two decades, infection remains a major cause of morbidity and mortality in neutropenic cancer patients. The concept of preventing infection in these patients with prophylactic antibiotic therapy was frowned on by many infectious disease experts when it was first introduced in the early 1960s, and it is still questioned by some. The first attempt at infection prophylaxis was a randomized trial of tetracycline given orally, which drug proved to be ineffective.[1] The various approaches subsequently used have been reviewed by Beutler, Barth and Bayer in this issue. Some of these approaches may be more or less controversial than this review suggests.

The development of the plastic tent isolator by Matthews gave impetus to attempts to "sterilize" neutropenic patients.[2] At first, a regimen of rotating nonabsorbable antibiotics was used because of the concern that organisms comprising the patients' endogenous microbial flora might develop resistance if exposed continuously to the same antibiotics. We then found that this was unnecessary and introduced the gentamicin-vancomycin-nystatin regimen.[3] Actually, vancomycin was included not only for its activity against Gram-positive cocci, but also because it has activity against many anaerobes.[4] It is perhaps fortunate that vancomycin was included in this regimen because pseudomembranous colitis did not become a problem in these patients. There can be no question that protected-environment units plus prophylactic antibiotic administration significantly reduce the risk of infection in neutropenic patients. This program also permits the administration of higher doses of chemotherapy. Unfortunately, administering higher doses of chemotherapy has not been shown to substantially improve the therapeutic results in patients with several types of malignant diseases. As Beutler and colleagues have pointed out, however, the use of autologous bone marrow transplantation permits the administration of much higher doses of chemotherapy and a protected environment-prophylactic antibiotic program is useful for patients receiving such therapy.[5] The controversy here is whether the benefits from this program justify the extra effort and expense, a point that has not been resolved.

Randomized trials of "gut sterilization" regimens administered to patients in conventional hospital rooms have produced conflicting results. Institutions using these regimens extensively eventually have been plagued with infections caused by resistant organisms. This has not been a problem when these regimens are given only to patients in protected-environment units because of the barrier between patients and the hospital environment. The introduction of trimethoprim-sulfamethoxazole has rekindled interest in antibiotic prophylaxis and most prospective randomized trials have found that this drug reduces the frequency of infection in neutropenic patients.

Van der Waaij and co-workers[6] have proposed that

it is important to devise regimens that preserve the anaerobic flora of the gastrointestinal tract. These organisms purportedly prevent colonization by potentially pathogenic Gram-negative bacilli. Although this has been shown in animals, it has never been shown to occur in humans. If "colonization resistance" exists, why do patients again become colonized by aerobic Gram-negative bacilli when the prophylactic antibiotics are discontinued? Some of the antibiotics that purportedly interfere with this "colonization resistance," such as some of the aminoglycosides, have no activity against anaerobic organisms. Most likely the beneficial effects of trimethoprim-sulfamethoxazole are due to its broad spectrum of activity, its excellent absorption from the gastrointestinal tract and its good penetration into body tissues. A prospective randomized trial showed that parenterally administered antibiotic agents that had a much lesser effect on the gastrointestinal flora were as effective as a gut sterilization regimen in reducing the risk of infection.[7] Furthermore, anaerobic coverage is probably unnecessary because anaerobes infrequently cause infection in neutropenic patients.

Beutler and colleagues have provided proper guidelines for the use of antibiotic prophylaxis. Not every neutropenic patient requires such prophylaxis. The risk of infection is related not only to the degree of neutropenia, but also to the duration.[8] Cancer patients with normal bone marrow who are expected to have chemotherapy-induced neutropenia of short duration do not need antibiotic prophylaxis. Exceptions are patients with other predisposing factors—such as bronchial or ureteral obstruction—and patients in whom more than one infection has developed previously when they were neutropenic. The routine use of trimethoprim-sulfamethoxazole must be discouraged because it has now been shown that colonies of resistant organisms may arise.

Reverse isolation has been shown to be ineffective and interferes with adequate patient care. This approach fails to protect a patient from potential pathogens, such as *Aspergillus* spp in the air and *Pseudomonas aeruginosa* in sinks. Washing of hands by personnel before and after touching patients is certainly important and physicians often fail to set an appropriate example. Some physicians have advocated that neutropenic patients should avoid eating fresh vegetables because these may be contaminated with Gram-negative bacilli, including *P aeruginosa*. The number of organisms in a meal portion is small, however, and whether or not uncooked vegetables are a major source of colonization has not been shown. It is estimated that a patient eating an average portion of tomato salad could ingest 5,000 *P aeruginosa* organisms. Studies of the intentional ingestion of *P aeruginosa* showed that fewer than 10,000 organisms were not detectable in feces. The selective pressure of antibiotic administration could affect colonization, however. Furthermore, we have found that even cooked foods handled in a routine fashion by a hospital kitchen may be contaminated by Gram-negative bacilli.

Removing intravenous lines within 48 hours as suggested by Beutler and colleagues may be desirable but is impractical for most patients who require prolonged intravenous administration of therapy. Maintenance of adequate venous access is most important in these patients and intravenous devices should remain in place as long as possible. Also, changing intravenous lines and bottles may introduce more contamination than it prevents.

Should neutropenic patients be immunized routinely? Beutler and colleagues advocate administering influenzal and pneumococcal immunizations to these patients. Certainly protection against influenza is desirable because this infection predisposes to bacterial infection. Both the malignant process and its therapy interfere with antibody responses, however, especially to primary antigens. Hence, immunization must be timed properly with chemotherapy to maximize antibody response, which is often difficult in patients receiving complex chemotherapeutic regimens. Pneumococcal immunization is more controversial. Pneumococcal infection has become an uncommon disease in many cancer centers. Whether or not immunization provides protection in these patients remains to be proved.[9] Pneumococcal immunization probably should be reserved for the most susceptible patients, such as elderly patients, those with chronic lung disease and those undergoing splenectomy.

The role of granulocyte transfusions has become unnecessarily controversial. For a variety of reasons, they are ineffective for prophylaxis of infection. However, there can be no question about their therapeutic efficacy when used appropriately. Because at least 50 percent of neutropenic patients in whom bacterial infections develop will respond to appropriate antibiotic therapy, they do not require granulocytic transfusions. Only patients with bacterial infections who are not responding to appropriate antibiotic therapy after two to three days require granulocytic transfusions. The dose of granulocytes is critical and optimum results require the transfusion of at least 10 billion cells.[10] Obviously, patients whose bone marrow will recover in a few days probably would also recover from their infection without granulocyte transfusions, but some could die in the interim. Often a physician cannot predict the speed of recovery of the bone marrow. On the other hand, patients who have prolonged neutropenia are subject to repeated infections and ultimately die, often of fungal superinfection. Because it is usually impossible to administer granulocyte transfusions for more than a week, it is unrealistic to expect that granulocyte transfusions would favorably affect more than the immediate infection in these patients. Also, if these latter patients suffer major organ dysfunction that is irreversible, the outcome cannot be favorably influenced by granulocyte transfusions. It is unfortunate that this lifesaving therapeutic modality has become a subject of controversy due to poorly designed studies. Randomly selecting neutropenic patients to receive or not receive inadequate doses of granulocyte transfusions routinely at the onset of fever is not an appropriate study design.

Certainly physicians must use every means at their

disposal to reduce the risk of infection in neutropenic patients. For patients who are expected to have only transient periods of neutropenia, instruction about the importance of prompt attention to fever is usually adequate. Current prophylactic measures for patients with prolonged neutropenia are suboptimal. As Beutler and colleagues mention, the use of immune modulators and the J5 vaccines may prove to be more effective approaches to infection prophylaxis.

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Case Reports

Prolactinoma in a Man Following Industrial Exposure to Estrogens

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THE CAUSE of pituitary tumors that secrete excess amounts of prolactin (prolactinomas) is uncertain, but there are substantial clinical and experimental data suggesting that estrogen may have an etiologic role.[1-5] A temporal link has been observed between the manifestations of hyperprolactinemia and estrogen-containing oral contraceptive use and childbirth.[1-5] However, others have observed only an equivocal temporal relationship between use of oral contraceptives and clinical presentation of prolactinomas.[6-10] In this report we describe a remarkable temporal relationship between industrial exposure to estrogen and the onset of hyperprolactinemia secondary to a prolactinoma in a man. To our knowledge, this is the first report of a temporal link between estrogen and the development of a prolactin-secreting pituitary tumor in a man.

Report of a Case

The patient, a 61-year-old man, was formerly employed by a pharmaceutical company that manufactures oral contraceptive pills. As a senior processing operator from 1971 to 1974, his duties included weighing and mixing norethindrone and mestranol, transporting the chemicals to and from mixing drums, ovens, storage facilities and tablet presses, and milling the chemicals into fine particles. During this work, he and his coworkers wore protective nylon suits and head coverings, but when they removed the garments they came into contact with the fine particles. Before beginning this particular job, the patient was told that he might develop "tender breasts." Of the dozen or so employees in his department, he noted that in most (both male and female) breast tenderness, "lumps" or enlargement developed. Furthermore, the patient knew of at least one male employee who had a mastectomy for breast enlargement.

Between 1972 and 1974, the patient noted bilateral breast swelling and nipple tenderness, and had intermittent episodes of impotence and diminished libido. In 1974 he complained of galactorrhea and gynecomastia, and was transferred to another department within the company. However, galactorrhea and gynecomastia persisted and in November 1975 a bilateral simple mastectomy was carried out. A prolactin level before the operation was 66 ng per dl. Because of the persistence of impotence and diminished libido, the patient was reevaluated in April 1976. Laboratory studies at that time gave the following values: thyroxine, 8.1 μg per dl; triiodothyronine, 167 ng per dl; thyroid stimulating hormone, 4.9 μU per ml; serum testosterone, 505 ng per ml; 24 hour urine study for 17-hydroxysteroids and ketosteroids, 7.6 mg and 5.7 mg, respectively, and serum prolactin, 68 ng per ml (normal, less than 30). Polytomography of the sella turcica showed an erosion in the floor of the sella into the left sphenoid sinus.

In September 1976 a transsphenoidal adenectomy

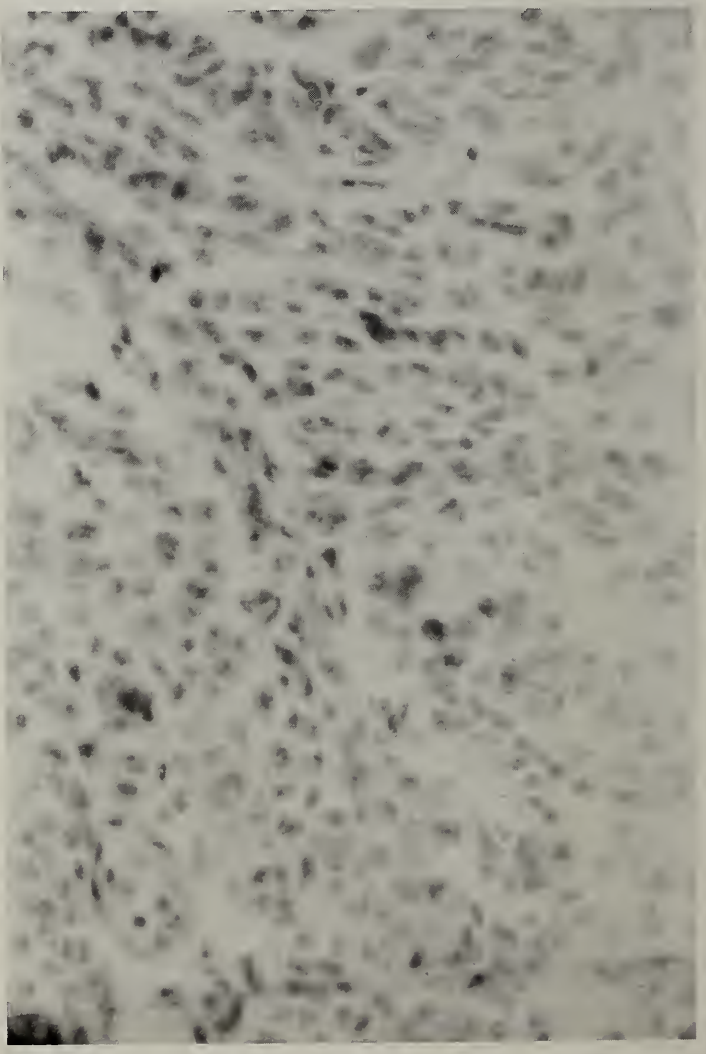

Figure 1.—Microscopic appearance of a prolactinoma in a man with clinical manifestations of hyperprolactinemia following industrial exposure to estrogens (reduced from ×200).

Refer to: Baron SH, Sowers JR, Feinberg M: Prolactinoma in a man following industrial exposure to estrogens. West J Med 1983 May; 138: 720-722.

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was done. A microadenoma was seen and removed along with a rim of pituitary tissue. Viewed microscopically, the pituitary tissue contained a diffuse area of tumor composed of a single cell type; the cells had normal to oval nuclei with indistinct agranular cytoplasm (Figure 1). The cells were periodic acid-Schiff negative and the tumor was classified as a chromophobe adenoma. After the operation diabetes insipidus developed in the patient but subsequently resolved. He regained potency and libido within six months. He had normal anterior pituitary function postoperatively.

Discussion

Although we do not have absolute proof that the development of a prolactinoma in this man was caused by estrogen exposure, there is considerable evidence supporting such a relationship. First, the clinical manifestations of hyperprolactinemia occurred after estrogen exposure. Before this exposure he had had no galactorrhea, gynecomastia or sexual dysfunction. He had taken no medication and had no other diseases[8] that could account for the symptoms. Furthermore, it appears that the galactorrhea, impotence and diminished libido were related to the hyperprolactinemia, as the latter two symptoms disappeared following hypophysectomy. Decreased libido and impotence are well-documented manifestations of hyperprolactinemia in men.[11] The bilateral mastectomy precluded observation of any relationship between the prolactinoma and galactorrhea.

Data from large series of patients with prolactinomas suggest a circumstantial relationship between estrogen use and prolactinomas. Molitch and Reichlin compiled data from 14 separate series and noted that of the patients with prolactinomas in whom previous oral contraceptive use could be ascertained, more than half the patients (189 of 363; 52.1 percent) had received oral contraceptives.[1] In some series, the percentage of tumor-bearing patients exposed to oral contraceptives reached 60 percent to 80 percent.[2-5] Sherman and his associates have concluded that exogenous estrogens or estrogen secreted during pregnancy may have a stimulatory effect upon the growth of clinically silent prolactinomas in some patients.[4,8]

That estrogen administration to humans leads to hyperprolactinemia has been documented in hypogonadal[12] and eugonadal[13] females. During the hyperestrogenic state of pregnancy, hypertrophy and hyperplasia of pituitary lactotrophs occurs.[14,15] Although ours is the first report of a link between estrogens and prolactinoma development in a man, there has been a report of a man who took estrogen for a year in whom galactorrhea, oligospermia and hyperprolactinemia (45 to 83 ng per ml) developed but who had no radiographic evidence of a pituitary tumor and whose prolactin levels declined following cessation of estrogen administration.[16]

There is substantial evidence that estrogen not only enhances prolactin secretion but also induces pituitary growth in animals. The former action of estrogen may be due to both a direct pituitary effect as well as an indirect effect via the hypothalamus to inhibit prolactin inhibitory factor. For example, estrogen has been shown in rat and ovine pituitary tissue to increase the incorporation of precursors into prolactin,[17-19] the accumulation of preprolactin in ribonucleic acid (RNA)[18-20] and prolactin synthesis.[18-22] In addition to these direct stimulatory effects upon the pituitary, estrogen decreases prolactin-inhibiting activity[23] and the release of the prolactin-inhibiting factor dopamine.[24] In regard to pituitary growth, a single injection of diethylstilbestrol into male rats is associated with pituitary hyperplasia or tumor in 70 percent of the animals.[25]

Conclusion

We believe there is reasonable clinical and experimental evidence suggesting a causal relationship between our patient's exposure to estrogens and the development of a prolactinoma. Thus, estrogen exposure may have either initiated tumor growth, or stimulated growth of a clinically silent microadenoma. That clinically silent pituitary microadenomas are not uncommon has recently been documented in an autopsy series.[26] Our case report emphasizes the fact that men, as well as women, exposed to industrial or other sources of estrogens need to be under surveillance for the development of clinical manifestations of hyperprolactinemia and pituitary tumors. Finally, measures to reduce industrial exposure to estrogens appear to be warranted.

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Noninvasive Diagnosis of Left Atrial Myxoma

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WITH THE ADVENT of M-mode and two-dimensional real-time echocardiography, the diagnosis of intracardiac tumors has commonly been made preoperatively and antemortem.[1-9] Several other noninvasive tests such as gated radionuclide cardiac imaging and computerized tomography (CT) scanning have been used.[10,11] We report the case of a patient in whom an abnormality was first considered from review of the chest films and the diagnosis confirmed by a two-dimensional echocardiogram and supported by dynamic CT scanning.

Report of a Case

A 44-year-old woman first presented to Stanford University Medical Center 16 years ago with Hodgkin's disease. She was staged as IIIA with bilateral cervical, supraclavicular, mediastinal and abdominal paraaortic node involvement. Treatment with low-dosage radiotherapy (total, 3,000 rads) to the affected lymphatic regions was successful, and she remained without evidence of disease when seen for yearly follow-up through October 1980. Although asymptomatic, her chest roentgenograms from 1978 through 1980 showed features of progressive pulmonary vascular congestion and enlargement of the main pulmonary artery. The diagnosis of congestive heart failure with secondary pulmonary hypertension was considered, as well as the possibility of recurrent mediastinal or hilar Hodgkin's disease masquerading as heart disease. Oral administration of furosemide was empirically begun. Conventional three-second CT scanning through the thorax showed no evidence of lymph node enlargement or tumor. The patient was referred to the Cardiology Division for evaluation of the cardiopulmonary abnormalities seen radiographically. She said she had no specific cardiac symptoms of congestive heart failure, syncope or chest pain. In addition, she stated she did not have weight loss, anorexia, fever, chills, rash or arthralgias.

On physical examination she was afebrile and had a heart rate of 100, blood pressure of 120/74 mm of

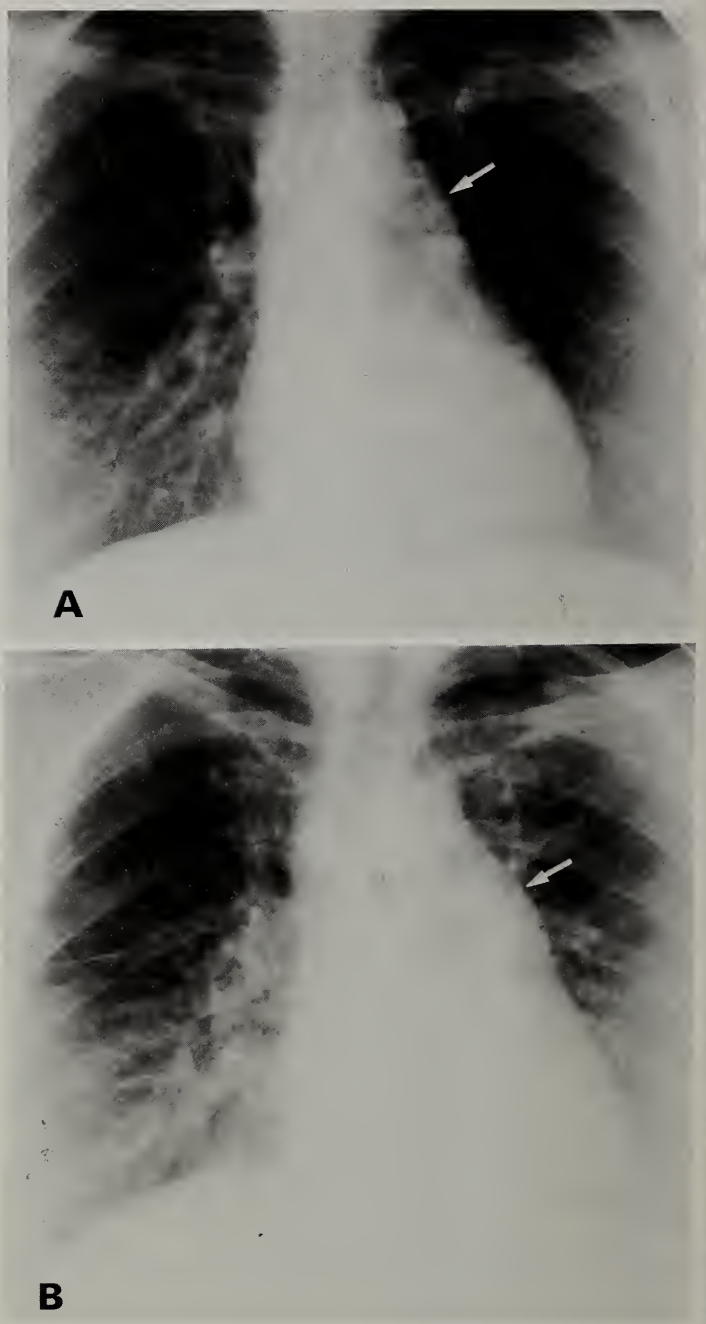

Figure 1.—Chest radiograph taken in September 1978 shows **(A)** the early changes of pulmonary venous hypertension with reversal of pulmonary blood flow to the upper zones and lack of clarity of the lower zone pulmonary vessels. Fullness of the pulmonary artery segment is evident **(arrow). (B)** Chest film in October 1980 shows changes of interstitial pulmonary edema indicating progression of pulmonary venous hypertension. Pulmonary artery segment has enlarged further **(arrow).**

Refer to: Echt DS, Guthaner DF, Blank N, et al: Noninvasive diagnosis of left atrial myxoma. West J Med 1983 Apr; 138:722-725.

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mercury and respiratory rate 18 per minute. No jugular venous distention was noted. The lungs were clear to auscultation and percussion. The point of maximum impulse was in the midclavicular line, S1 and S2 were of normal intensity and a grade 2/6 systolic ejection murmur was heard best at the lower left sternal border and radiated to the left upper sternal border. Her extremities did not have edema or skin lesions.

Laboratory studies were notable for the following values: hematocrit, 37.8 percent; leukocyte count, 7,200 per μl; erythrocyte sedimentation rate, 39 mm an hour, and platelet count, 242,000 per μl. The chemistry levels were all within normal limits. Twelve-lead electrocardiography showed a sinus tachycardia with early R-wave transition across the precordium.

Chest radiography showed evidence of pulmonary venous hypertension with the presence of interstitial changes in the lung fields, prominence and indistinctness of the hilar shadows, reversal of pulmonary blood flow to the upper zones and enlargement of the main pulmonary artery (Figure 1). The left atrium did not appear enlarged. On reviewing the chest films from an examination with normal findings done six years previously, the main pulmonary artery segment was found to have gradually enlarged to produce a straightening of the left cardiac contour in 1978 and had progressed to a convex contour seen on the current film. In retrospect, reversal of pulmonary blood flow was evident even on the 1978 film (Figure 1). A year before presentation subtle interstitial changes were already evident. The review of the chest films prompted further investigation for a possible cardiac disorder.

The initial two-dimensional echocardiogram showed a homogeneous, poorly reflective large mass in the left atrium. The mass moved toward the mitral orifice during diastole. The point of attachment between the mass and the atrial wall could not be identified on this first study. The apical phonocardiogram confirmed the presence of a midsystolic ejection murmur of low intensity.

On the basis of the above test findings, a preliminary diagnosis of an atrial tumor was made and the patient was admitted to hospital. Echocardiography was repeated using a prototype dynamically focused, electronic phased-array instrument (Hewlett-Packard 77020A). A short stalk was seen to arise from the interatrial septum, near the fossa ovalis, and to extend to the mass (Figure 2). On this basis a diagnosis of atrial myxoma was advanced.

A dynamic CT scan was carried out for our interest because the initial CT scanning was not cardiac directed and did not show a cardiac lesion. The dynamic modification augmented maximal opacification of the left atrium following intravenous administration of a bolus of contrast medium. A filling defect was seen through the midportion of the left atrium (Figure 3). The tumor extended superiorly to encroach on the right superior pulmonary vein.

Coronary angiography was not done as the patient was relatively young and asymptomatic. She was taken to the operating room for thoracotomy and surgical excision of the tumor without further studies. On opening the left atrial chamber, a 5.7 by 4 cm soft, gelatinous, rubbery tumor was found attached to the interatrial septum in the region of the fossa ovalis by a 2-cm stalk. No tumors were found on inspection of the other cardiac chambers. The tumor and the interatrial septum at the point of attachment were removed. The atrial-septal defect so produced was repaired by oversewing. Routine histologic examination showed that the tumor

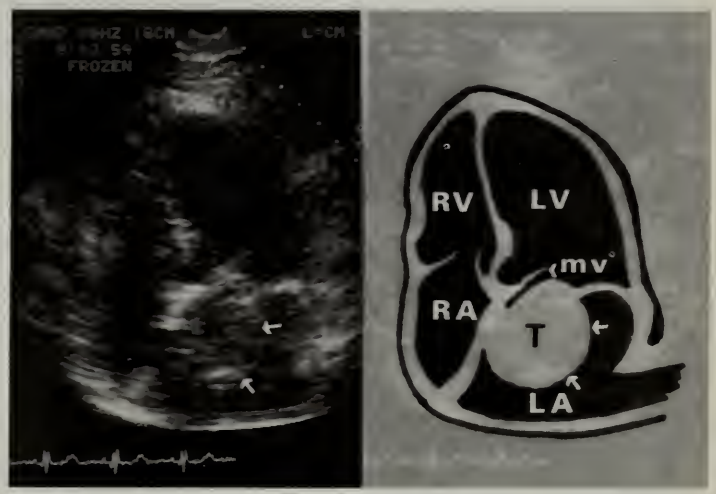

Figure 2.—Apical four-chamber view of the ultrasonic two-dimensional echocardiographic image from the patient (left panel). The mass of echoes **(arrows)** within the left atrium (LA) moved with the cardiac cycle and seemed attached to the interatrial septum as diagrammed in the right panel. LV = left ventricle, MV = mitral valve, RA = right atrium, RV = right ventricle, T = tumor.

Figure 3.—Computerized tomographic scan from a dynamic series taken through the level of the mid left atrium (LA) and portion of the aortic root following a peripheral intravenous bolus injection of contrast demonstrates a circular filling defect within the LA **(arrows)**. RA = right atrium, RVOT = right ventricular outflow tract, LV = left ventricle, PV = pulmonary veins, DAo = descending aorta, Ao = aortic root.

was typical of atrial myxoma. The patient recovered without complications.

Comments

This patient presented without symptoms, but the progressive development of rather subtle signs of pulmonary venous hypertension seen on the chest films provided the first (nonspecific) clue to the diagnosis. Chest radiography for the diagnosis of atrial myxoma has not received much attention recently since the development of more definitive diagnostic tools. A review of nine patients studied by cardiac fluoroscopy after swallowing barium solution showed mild left atrial enlargement in all patients who had left atrial myxoma.[12] All but one patient had evidence of pulmonary venous distention. Similar results were found in a series of 40 patients.[9] These findings are indistinguishable from patterns seen in mitral stenosis.[13] Calcification of a myxoma is occasionally appreciated but this is more common with right atrial myxoma.[14]

The initial routine thoracic CT scanning, done to exclude the possibility of recurrent Hodgkin's disease, did not show an intracardiac tumor. Cardiac involvement with Hodgkin's disease has been reported.[15] However, the occurrence of a pedunculated intracavitary mass as the *only* manifestation of recurrence would be exceedingly rare and has not been reported to the best of our knowledge.

On the initial M-mode echocardiogram there were multiple echoes in the left atrial cavity, suggesting a homogeneous mass. Care must be taken in diagnosing a mass on this basis alone. This patient's M-mode study of the mitral valve region did not show the stack of echoes appearing just after mitral opening behind the anterior mitral valve leaflet that has become the echocardiographic hallmark of left atrial myxoma. Such absence of echoes behind the anterior mitral leaflet may occur because a tumor does not extend far into the mitral channel during diastole. This may apply to small tumors with short pedicles, sessile tumors or very large ones that cannot fit within the mitral valve orifice. In this case, the tumor was probably larger than the mitral valve orifice. The first two-dimensional echocardiogram done on this patient showed findings highly suggestive of an atrial myxoma. The mass was not defined clearly enough, however, to warrant ablative therapy without further diagnostic evaluation. Findings on the second echocardiogram done on a different instrument were convincing. The two-dimensional echocardiogram, particularly in the apical four-chamber view, showed the tumor with a high degree of certainty. Information about the size, mobility, effect on cardiac function, presence of a pedicle and site of attachment was obtained. These are the findings required before a surgical procedure. As suggested by Lappe and co-workers,[7] if this information can be obtained by echocardiography or other noninvasive means, angiography is not necessary. In this premenopausal woman we assumed a low probability of coronary artery disease. In seven other patients we have done coronary angiography only before tumor removal.

The diagnosis of atrial myxoma has been reported using routine thoracic CT scanning, without the means of controlling cardiac motion artifacts.[16] The filling defect of a tumor can be recognized on routine scanning through the chest. In this patient, routine scanning failed to identify the tumor, probably because of the presence of artifacts and scan levels not chosen to pass through the mid left atrium specifically. The second CT scanner used in this case is a third-generation scanner, dedicated for research, with the potential for gated and dynamic scanning. The scanning done—dynamic but not gated—gave clear images that confirmed the presence of the mass.

Gated nuclear scanning has been used in recent years to complement echocardiography. In one series six of seven scans were reported positive for an intracardiac tumor in patients with echocardiographic evidence of an atrial myxoma later confirmed with both angiography and surgical excision.[10] Gated nuclear scanning is less sensitive than echocardiography due to low resolution but, when positive, may provide additional support of a diagnosis.

Left atrial angiography via pulmonary artery contrast injection has been the definitive diagnostic mode in the past. An intracavitary filling defect is the most common finding.[13,17] Other indirect evidence includes compression or displacement of large vessels, abnormalities of the cardiac chamber and pericardial effusion.[13] The exact incidence of false-positive and false-negative findings on angiograms has not been determined. Intraatrial thrombi, intraatrial hematomas and failure to recognize streaming of nonopacified blood are the most common causes of false-positive findings. Pulmonary artery injection also carries increased risk of morbidity and mortality in the presence of severe pulmonary artery hypertension. With transseptal left atrial catheterization, there is the risk of peripheral embolization of tumor fragments. The site of tumor attachment is seldom found by angiography.

Since the recurrence of tumor has been reported, many surgeons now excise the interatrial septum at the attachment of the pedicle, as was done in this patient. Even with this precaution, tumor recurrence has been occasionally reported.[18] Postoperatively, echocardiography frequently shows an abnormal appearance at the site of repair of the atrial septum. We routinely do baseline echocardiography postoperatively before discharge for later comparison should symptoms redevelop. Recurrence is unusual, so we do not routinely do late follow-up echocardiography.

Only since the advent of echocardiography has atrial myxoma been diagnosed routinely before death. Tumors that produce perfectly classic and typical echocardiographic images of an intraatrial mass, attached to the interatrial septum by a stalk, may provide a physician with a sufficiently confident diagnosis to proceed to surgical intervention. In less optimal situations ad-

ditional supportive information may be required. Gated nuclear scanning, cardiac CT scanning or traditional contrast angiography may be used as indicated by local expertise.

Summary

An asymptomatic woman previously successfully treated for Hodgkin's disease, stage IIIA, was found by echocardiography to have a left atrial myxoma and the diagnosis was supported by other noninvasive tests. This case serves to emphasize four main points. First, high-resolution two-dimensional echocardiography is an effective tool for finding intracardiac tumors. Second, the tumor may be recognized on computerized tomographic scans with deliberate searching. Third, consideration of surgical excision without prior angiography is justifiable in selected cases. Finally, we would like to emphasize that the astute interpretation of the plain chest radiography initiated further investigation.

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Transient Global Amnesia: A Common, Benign Condition

The Need for Exact Diagnostic Criteria

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MANY DISORDERS of diverse type may affect the central nervous system, resulting in loss of recent memory that may be either transient or permanent. If we exclude the most common causes of recent memory loss (for example, blunt trauma to the head, alcoholic "blackout," Wernicke's encephalopathy), it is possible to recognize another distinct clinical amnesic disorder. Although alarming to patients and their families, this amnesia is nearly always benign, rarely recurs and almost never evolves into a complete stroke. First recognized by Morris Bender[1] in 1956, the disorder was named *transient global amnesia by* C. Miller Fisher and Raymond Adams[2] two years later. Before their reports, these episodes were commonly thought to be of "hysterical" origin, though migraine and temporal lobe epilepsy were also suggested as possible causes.

In Table 1 is a list of the clinical features that permit a reasonably confident diagnosis of transient global amnesia, though the condition often requires diagnosis by exclusion. We have had the opportunity to examine six of these patients in the past two years at a 200-bed general hospital (which admits about 1,200 patients per month) or at the associated outpatient clinics, which see about 40,000 patients per month. Table 2 is a summary of the clinical data for these six patients, who have been followed for up to 2½ years without similar recurrence nor with more typical (sensorimotor) symptoms of a stroke developing.

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Report of a Case

A 62-year-old woman, a Sunday-school teacher, was examined within 18 hours after she had an episode of total loss of recent memory—transient global amnesia —for a period of five hours early in 1982. The memory loss occurred abruptly, without warning, in the setting of teaching three classes from 9 AM to noon. None of her pupils (children or adults) noted any bizarre behavior, physical distress or deviation from her usual speech or command of her material during this period, which included question-and-answer sessions for each class.

The patient was driven to the classes (without accident or event) and remembered what she had for breakfast but without referring to prepared notes was unable to recall what she said or did in the forenoon at school.

At about 1 PM she began repeatedly asking her fellow teachers who and where she was, much to their astonishment because she did not otherwise appear ill. Her confusion gradually cleared during the next three hours so that by 4 PM she felt "in command of [her] senses completely." During this second phase, she recognized familiar faces, places and things. She felt much relieved to hear that she had apparently taught her classes with her usual skill and had evinced no unusual behavior or language disturbance.

The patient has had no recurrences of transient

global amnesia since, nor had she experienced such an episode previously. No risk factors for stroke were identified in her, but both parents had had stroke syndrome (her father had died at age 99 years, her mother at 81) and a sister had died at age 77 years of a myocardial infarction.

Results of a neurologic examination, including speech and memory evaluation, were normal. Spinal tap, cerebrospinal fluid analysis, electroencephalogram, x-ray films of the skull and chest, electrocardiogram, radionuclide scan and flow test results were all normal. Results of computerized tomography (CT) scan (with and without contrast) done five days after the episode of transient global amnesia were also normal.

At reevaluation three months later, she reported no transient ischemic attacks or further episodes of amnesia. Results of general medical and neurologic examinations were normal; specifically, she showed no language, visual field or memory deficits.

Discussion

For the past 30 years, published works in neurology and neurosurgery have repeatedly stated that human memory disorders result from lesions of the medial temporal lobe(s) and specifically from damage to the hippocampus and its central connections. In 1962 Whitty[3] conceived a dual anatomic basis for memory: limbic-system neurons (in hippocampus fornix-mamillary bodies, anterior thalamus) are responsible for new learning, and cortical neurons in the temporoparietal and occipital lobes are responsible for storage and retrieval. In 1964 Victor and co-workers[4] emphasized that although the anatomy of memory is extremely complex, memory loss occurs only with bilateral hippocampal lesions. In 1978, however, a serious criticism of this classical hypothesis was advanced by Horel[5] as a result of ablation experiments in monkeys. He suggested that the lesion producing the amnesic syndrome resulted from interruption of white matter tracts in the medial temporal lobe referred to by anatomists as the "temporal stem-albal stalk." Through this region pass afferent and efferent connections of the temporal cortex and amygdala but not the hippocampus or its associated fornix-mamillary body system (Figure 1), according to Horel.

The underlying pathology is presumably vascular[6,7]

TABLE 1.—*Ten Essential Features of Transient Global Amnesia*

No premonitory TIA
Risk factors for stroke often absent
Isolated severe loss of recent memory (<24 hr)
Complete clearing once episode has passed
Patient aware/anxious about deficit
Sparing of motor, visual and speech systems
No change in personality
Persistence of unimpaired technical skills
Rarely evolves to more characteristic stroke
Rarely recurs

TIA = transient ischemic attack.

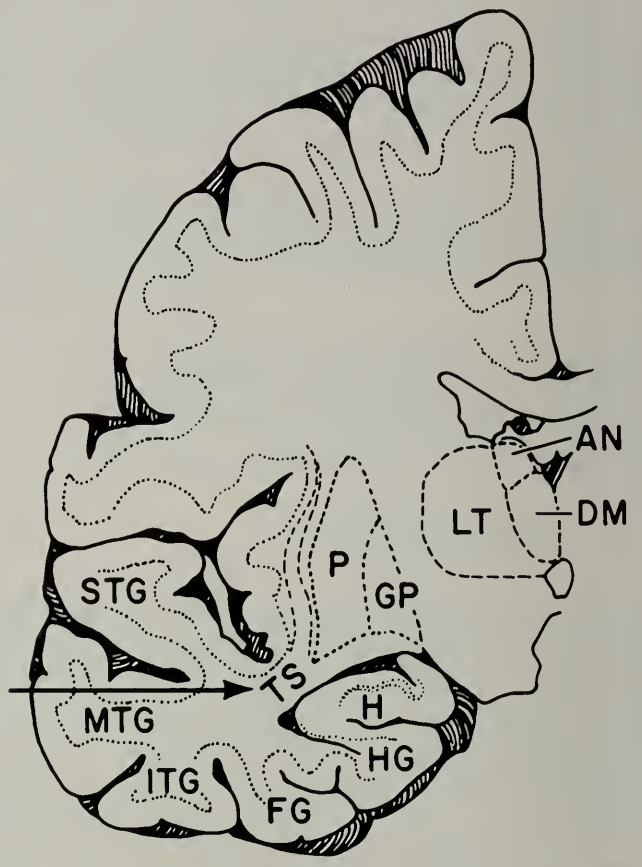

Figure 1.—The hippocampus and temporal stem. AN = anterior nuclear group; DM = dorsomedial nucleus; FG = fusiform gyrus; GP = globus pallidus; H = hippocampus; HG = hippocampal gyrus; ITG = inferior temporal gyrus; LT = lateral thalamus; MTG = middle temporal gyrus; P = putamen; STG = superior temporal gyrus; TS = temporal stem. (Modified from Horel.[5[p405]])

TABLE 2.—*Clinical Data for Six Patients Who Had Transient Global Amnesia*

Patient	*Age/Sex/ Occupation*	*Stroke Risk Factors*	*Duration of Episode (hours)*	*Scans Nuclide/CT*	*Follow-up Without Recurrence or CVA (months)*
1	55/♀/Housewife	No	15	N/N	36
2	66/♂/Realtor	No	<24	N/N	12
3	62/♂/Engineer	No	2	N/—	33
4	62/♀/Teacher	Yes	7	N/N	16
5	66/♂/Locksmith	Yes	24	—/N	25
6	75/♀/Housewife	Yes	20	N/—	10

CT = computerized tomography; CVA = cerebrovascular accident; N = normal.

in origin, though careful dissections and vessel injections after death are few.[8] The vessel(s) involved are the sylvian branches of the posterior cerebral arteries supplying the posterior ventromedial quadrants of the temporal lobes. Lesions at that location do not interfere with propositional speech, hearing, reading, remote memory or visual fields nor, most remarkable, with highly developed technical skills or with the ability to recognize familiar faces (that is, *prosopagnosia*). Thus, Byer and Crowley[9] reported the case of an organist who was able to perform a recital flawlessly despite a coincident episode of transient global amnesia.

Apart from anxiety due to awareness of the deficit, patients with transient global amnesia do not have the characteristic symptoms of the Klüver-Bucy syndrome,[5] for example, psychic blindness, first described in 1938.[10] This syndrome has been reproduced in monkeys by bilateral temporal lobectomy or by destruction of one temporal lobe, of the contralateral occipital lobe, and cutting the splenium of the corpus callosum.

We suggest that if a clinician obtains a medical history characteristic of transient global amnesia in a patient, skull x-ray evaluation or cerebrospinal fluid examination is superfluous. The percentage of abnormal findings on radionuclide scans, angiograms and electroencephalograms varies greatly from patient series to series. A careful medical and neurologic examination supplemented by a CT scan and regular follow-up examinations can suffice to establish the diagnosis in most patients suspected of having transient global amnesia. Their gratitude (and the relief of their families) that they are probably not dealing with a progressive or threatened stroke or malignancy provides justification that a clinician be aware of this subtype of the far more common entity, transient ischemic attack with amaurosis fugax, or fleeting sensorimotor deficits.

Finally, the classically accepted role of the fornix-mamillary bodies of the hippocampus in the memory process is questioned on the basis of careful studies in a limited number of monkeys reported by Horel[5] in 1978. This theory correlates with the suggestion of Victor and associates[8] that damage to certain thalamic nuclei is responsible for the characteristic memory deficit in Korsakoff's (alcoholic) psychosis.

Mathew and Meyer[11] have emphasized that recurrent episodes of transient global amnesia (not seen in our smaller series) imply an increased risk of dementia with permanent loss of memory or what they term an "amnesic stroke" (that is, sensorimotor deficit developing in the setting of one or more amnesic attacks).

Summary

The cases of six middle-aged patients with characteristic symptoms of transient global amnesia have been followed. We emphasize the importance of recognizing this rather common clinical entity as benign (that is, unlikely in our experience either to recur or to evolve into a more characteristic hemiplegic stroke).

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Toothpick Perforation of the Inferior Vena Cava

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TOOTHPICK PERFORATION of the duodenum into the inferior vena cava is a medical curiosity. The following case, however, illustrates several points of general interest. First, when multiple Gram-negative organisms are cultured from the blood, an intraabdominal source of infection is likely to be present. Second, abdominal computerized tomographic (CT) scanning is an effective means of inspecting the retroperitoneum: it can detect small foci of infection that are not apparent on plain films of the abdomen and thus aid in diagnosing inferior vena caval thrombosis. Finally, suppurative thrombophlebitis is best treated by vein excision.

Report of a Case

A 45-year-old rancher was admitted to a Sacramento Valley (California) hospital because of fever, chills, weakness and abdominal pain for four days. Previously his health had been excellent, although he did say that he had been drinking half a bottle of scotch a day for many months. On admission, physical examination showed a confused middle-aged man with a temperature of 37.6°C (99.7°F). Aside from mild epigastric tenderness, physical findings were unremarkable. Admitting laboratory studies disclosed the following values: hematocrit, 47 percent; leukocyte count, 12,000 per μl with toxic granulations; albumin, 3.1 grams per dl; total bilirubin, 0.6 mg per dl; alkaline phosphatase, 138, serum aspartate aminotransferase (formerly SGOT), 83 and amylase, 203 IU per liter, and stool guaiac, trace positive.

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Submitted May 4, 1982.

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A diagnosis of alcoholic pancreatitis was made and the patient was treated with nasogastric suction and fluids administered intravenously. On the third day of his hospital stay, the patient became febrile to 40°C (104°F) and broad-spectrum antibiotic therapy was started. Initial blood cultures were positive for group B *Streptococcus* but culture of a blood specimen drawn on the sixth hospital day, when the patient was receiving penicillin alone, grew *Escherichia hafnia*. Gentamicin therapy was reinstituted but, despite apparently adequate antibiotic coverage, the patient was persistently febrile and in a toxic condition during a nine-day hospital course. Analysis of urine, lumbar puncture, abdominal ultrasonogram, liver-spleen scan and upper gastrointestinal series showed no abnormalities. He was transferred to University of California, San Francisco, for further evaluation.

On admission, the patient's temperature was 39.8°C (103.6°F), pulse rate 125, blood pressure 95/55 mm of mercury and respirations 28 per minute. He was disoriented, but physical examination showed otherwise normal findings. Laboratory examination showed persistent leukocytosis and hyperamylasemia. In the ensuing week, there were daily temperature spikes to 40°C (104°F). Cultures of blood specimens drawn during antibiotic therapy grew five different organisms considered to be oral flora. They were identified as *Streptococcus intermedius, Eikenella corrodens, Bifidobacterium* sp, *Bacteroides melaninogenicus* and *Veillonella*. An abdominal CT scan done at the time of admission showed a diffusely enlarged pancreas without evidence of pancreatic abscess. A repeat abdominal CT scan on the ninth hospital day showed no change in the pancreas. However, additional views of the inferior vena cava were incidentally obtained. A low-density filling defect and air bubbles were seen in the infrarenal inferior vena cava (Figure 1). Based on these findings, a diagnosis of septic thrombosis of the inferior vena cava was made. Another chest x-ray film taken at this time showed multiple new pulmonary nodules, one of which showed central cavitation. A phlebogram of the inferior vena cava confirmed the presence of thrombus in the vena cava (Figure 2).

At operation the pancreas was firm and diffusely enlarged. The duodenum was densely adherent to the underlying vena cava. The remainder of the abdominal exploration gave normal findings. The vena cava was then resected from the iliac veins inferiorly to the renal vein superiorly. A toothpick was found in the distal portion of the specimen, surrounded by thrombus and extending into the left common iliac vein (Figure 3). Careful inspection of the reflected duodenum revealed a 2-mm perforation.

The iliac veins and vena cava were then oversewn

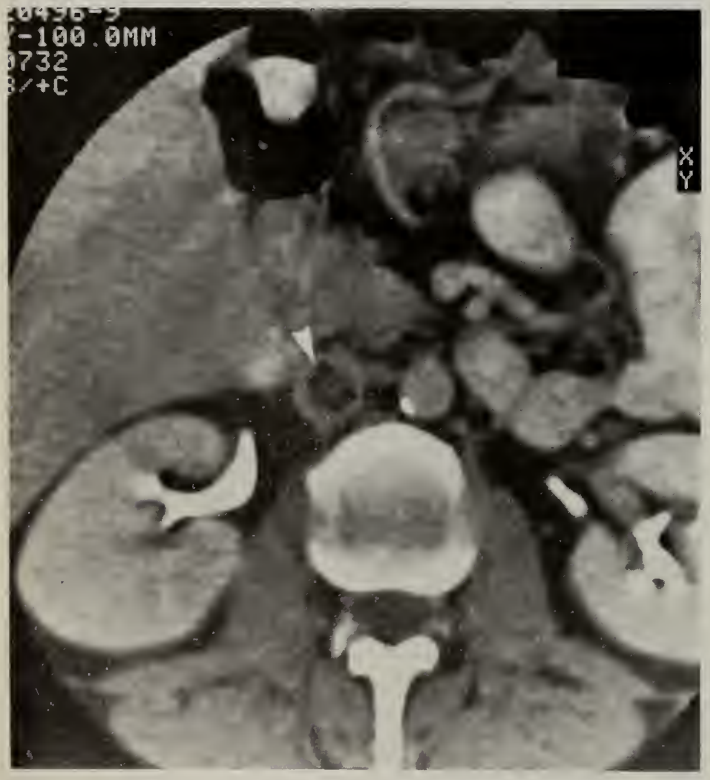

Figure 1.—A computerized tomographic scan of the midabdomen. The arrow points to the thrombus and the air bubbles in the inferior vena cava.

Figure 2.—An inferior vena cavogram confirming the presence of a thrombus.

with polypropylene sutures and the duodenum was repaired in two layers. Postoperative recovery was smooth. Antibiotic administration was continued for ten days and the patient promptly became afebrile. Chest films showed clearing of the pulmonary nodules.

The patient was discharged two weeks postoperatively and was doing well two months after discharge, with no venous insufficiency of the lower extremities. When questioned later, he recalled occasionally eating club sandwiches and hors d'oeuvres containing toothpicks, but did not remember swallowing a toothpick. He does not wear dentures but does admit to binge drinking.

Comments

Two previous cases of toothpick perforation through the duodenum into the vena cava have been reported.[1,2] In each instance, a one- to two-week history of abdominal symptoms, fever and chills preceded admission to hospital. Florid sepsis was evident at the time of admission, and blood cultures grew multiple organisms. Both patients died of overwhelming sepsis and at postmortem examination were found to have toothpicks lodged within a fistula between the duodenum and inferior vena cava.

Two other cases were similar to ours. A toothpick was discovered in the right ventricle during tricuspid valve replacement and pulmonary embolectomy in a patient who presented with *Candida* endocarditis and septic pulmonary emboli.[3] This man died of irreversible pulmonary hypertension and at postmortem examination had fibrous scarring and evidence of old hemorrhage near the duodenal-caval interface. Another patient died of streptococcal septicemia following fishbone perforation of the portal vein.[4]

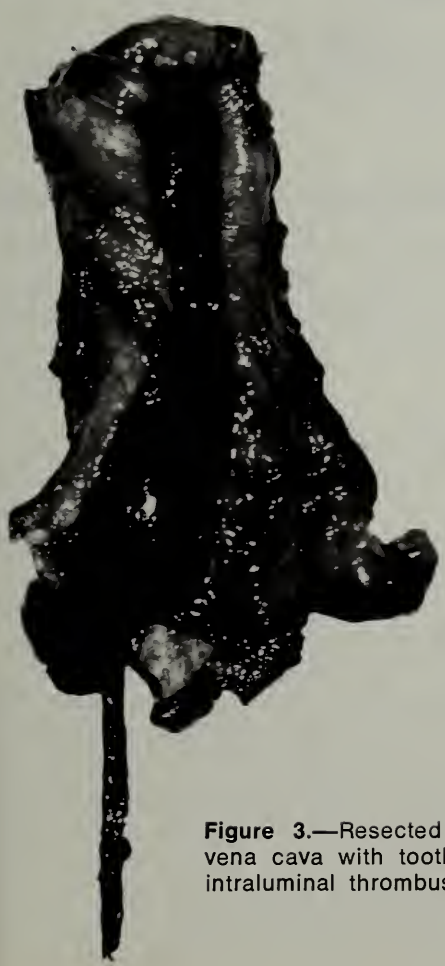

Figure 3.—Resected segment of inferior vena cava with toothpick extending from intraluminal thrombus.

These cases show the great difficulty of making a premortem diagnosis of toothpick perforation of the gastrointestinal tract.[5] Generally, patients cannot recall toothpick ingestion even if subsequently they admit to their use. Unlike other foreign bodies, such as metal objects and bones, toothpicks are not detected by standard x-ray studies. Perforation may occur into the retroperitoneum, and normal inflammatory responses may seal the injury. Free peritoneal air is seldom seen.[6]

Previous reviews have shown that ingestion of foreign bodies tends to occur in patients whose oral sensation is diminished because of excessive alcohol ingestion or the use of dentures.[5,7,8] Although about 80 percent of foreign bodies pass in the feces, sharp objects may arrest and perforate anywhere along the gastrointestinal tract. Points of angulation that may cause delay in passage of a foreign body include the junction of the second and third parts of the duodenum, the ileocecal valve, the appendix and the flexures and haustra of the large intestine.[9] Perforation of the upper gastrointestinal tract, which occurred in our patient, is a rare presentation. In one large series of intestinal perforations due to sharp foreign bodies, only 5 of 83 perforations occurred in the region of the stomach or duodenum, whereas 73 percent occurred in the ileocecal region.[10]

Computerized tomography recently has been found capable of detecting tumor invasion and thrombosis of the great vessels in the retroperitoneum. CT scans have correctly visualized renal, adrenal and testicular tumor extension into the renal veins and inferior vena cava, and thrombus has been shown below the level of an inferior vena cava umbrella placed for recurrent pulmonary emboli.[11,12] Indirect evidence of thrombosis may be seen as enlargement of the renal veins or inferior vena cava, whereas direct evidence may be obtained by CT scanning after a bolus injection of water-soluble contrast through a peripheral vein.[6] The incidence of false-positive or false-negative studies in these situations, however, is unknown. Computerized tomography remains a useful adjunct to traditional phlebography, providing noninvasive evaluation of the retroperitoneum.

In addition to the detection of thrombus, computerized tomography permitted the specific diagnosis of *septic* thrombosis of the inferior vena cava in our patient. The finding of intraluminal gas pockets was first described in four patients with infected Dacron aortofemoral bypass grafts.[13] In these cases and in one other case of subcutaneous emphysema of the leg due to toothpick perforation of the ileum,[14] gas may have been produced by bacteria or pushed into the retroperitoneum by gut peristalsis.

Septic thrombosis of central veins has been uncommon in the past but has occurred more frequently since

the advent of central venous catheters. Suppurative thrombophlebitis of the peripheral veins is most efficiently treated by excision of the involved segment.[15,16] Less accessible central veins have been treated with administration of antibiotics and anticoagulation.[17] Although experience is limited, septic pulmonary emboli or sepsis refractory to antibiotic therapy is the present indication for surgical intervention in suppurative central venous thrombosis. Excision of the infrarenal vena cava was well tolerated by our patient. Abundant collateral pathways through the left gonadal, the azygous and the inferior epigastric veins often prevent the development of lower extremity venous insufficiency.

Both new and traditional diagnostic methods led to a correct diagnosis of septic thrombosis of the inferior vena cava in our patient, and an aggressive surgical approach resulted in a rapid, dramatic cure with no significant morbidity. We believe this is the first successful treatment of this rare disorder.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgement before publication.

A Mystery Solved?

TO THE EDITOR: Dr Elliott B. Oppenheim, in his book review in the January issue,[1] mentioned that the title of *Mnemonics, Rhetoric and Poetics for Medics* by Drs Robert L. Bloomfield and E. Ted Chandler made no sense as a mnemonic, but I suspect it may in fact be a very subtle—even medieval—allusion.

Those of us who attended university during the Middle Ages recall that the seven liberal arts were divided into the *quadrivium*—arithmetic, music, geometry and astronomy—and the *trivium*—grammar, rhetoric and logic. Might not mnemonics, rhetoric and poetics be an allusion to grammar, rhetoric and logic? (Etymologists insist that the word "trivia" is *not* derived from the latter division of the medical curriculum.)

THOMAS STAIR, MD
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Washington, DC

REFERENCE

1. Oppenheim EB (reviewer), Bloomfield RL, Chandler ET: Mnemonics, Rhetoric and Poetics for Medics, book review. West J Med 1983 Jan; 138:127

Emergency Care in Albuquerque

TO THE EDITOR: The article by Dr Charles Bova ("The 'Request for Proposal' Approach to Designation of a Trauma Center")[1] in the January 1983 issue presents several viewpoints with which many Albuquerque physicians strongly disagree.

It is readily conceded that designation of a trauma center (at whatever level) in the rural areas of our state will likely reduce the rural trauma death rate. However, the need for and the supremacy of a single Albuquerque institution as a trauma center in Albuquerque, for the Albuquerque metropolitan area, has not been clearly established and was so indicated in the site visit team's recommendation. Many physicians feel strongly that the University of New Mexico Hospital offers little, if any, advantage over some other area hospitals with respect to ability to manage trauma. These physicians feel that the selection of UNM Hospital as a "trauma center" was based on bureaucratic bias and was politically motivated. As an example of bias, Dr Bova's statement that "Emergency services at the other regional hospitals are to be continued for minor trauma" is untrue. In reality, the Selection Committee stated that "the current pattern of trauma referral was not to be disrupted." UNM Hospital was given the responsibility to provide outreach education for the region; it was not given responsibility for all trauma patient care.

Although Dr Bova's article contains some valid concepts, many of us involved in emergency care in Albuquerque feel strongly that only one side of a complex issue was presented.

ROBERT C. HENRY, MD
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Albuquerque

REFERENCE

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Amanita phalloides Poisoning

TO THE EDITOR: Having followed *Amanita phalloides* literature for several years, combined with our own experience at Stanford, qualifies us to compliment the recent article by Kent R. Olson and co-workers[1] and amplify on three of its points.

First, we concur from personal experience and literature review that thioctic acid is probably of no additional benefit in the treatment of *Amanita* poisonings.

Second, all of our fatalities at Stanford over the past ten years had blood culture confirmation of associated Gram-negative bacteriemia. In treating critically ill patients who have eaten mushrooms, one has to constantly be aware of this potentially lethal complication.

Last, Dr D. Costantino's group at the University of Milan have published several well-controlled studies in the European literature during the past several years on the mechanisms of *Amanita* toxin clearance. Utilizing radioimmunoassay techniques, amatin toxin renal clearance curves and enterohepatic circulation patterns have been clearly defined. Application of this information to patient care in Milan has greatly enhanced survival rates and provided some scientific basis to the recommended treatment for the patients who have eaten *Amanita phalloides* mushrooms.

Until a true antidote can be found, we would agree with Costantino's recommendations. In the face of normal renal function, forced diuresis should be continued for the first 36 hours following admission. Concomitantly, to interrupt the enterohepatic circulation of the amatin toxin, charcoal is given by mouth hourly along with cathartics such as lactulose through the same 36-hour period. If the patient is a transfer patient and the

time of ingestion is longer than 48 hours from admission, then the forced diuresis and charcoal are probably of no therapeutic benefit.

In summary, rapid recognition in an emergency room of a person who has eaten *Amanita phalloides* mushrooms and initiation of early aggressive treatment maximizes the probability of a favorable outcome.

DONALD C. HARRISON, MD
Stanford, California
BRIAN T. PAASO, MD
Palo Alto, California

REFERENCE

1. Olson KR, Pond SM, Seward J, et al: *Amanita phalloides*-type mushroom poisoning. West J Med 1982 Oct; 137:282-289

The Future of Physician Assistants

To the Editor: If there is a lesson to be learned from reading the discussion section of the article "Training physician assistants for the Pacific Northwest—The MEDEX Northwest ten-year experience" by Harmon and co-workers,[1] it is that reducing complex manpower problems to simple solutions is hazardous.

Since 1972 government funds have been made available to support primary care physician assistant (PA) training programs because there was a shortage of physician manpower in the 1960s. According to the Graduate Medical Education National Advisory Committee (GMENAC) report by 1990 this situation will no longer exist. At that time this country will witness a physician glut. Many of these surplus physicians will set up practices in underserved areas, which up to now have been places of PA utilization. As the numbers of physicians increase, especially family physicians and primary care internists, they will as a matter of economic self-protection limit the scope of practice of any professional group seen as a potential competitive threat. The 1976 Health Manpower Assistance Act has already reduced the number of foreign medical graduates allowed into the country, helping to reduce physician oversupply. Will PA's be next in line to feel the competitive axe? The Washington State Medical Association has already withdrawn its endorsement of the MEDEX program, in anticipation of physicians competing for practice sites. Can this action be the start of a domino effect that will spread to other portions of the country? Will not the same narrative happen to PA's in Montana (which recently allowed PA practice) when enough physicians are available to fill the manpower void currently being felt? If so, were PA's invented to fill a temporary void in health manpower and now, like outdated pieces of technology, are to be cast aside? Should PA's continue to be envisioned in the same capacity as they were in 1972?

The lesson to be learned is that once a profession is invented to supply a need (PA's), and that need is filled (the oversupply of physicians), then other avenues of expression must be found for that profession. The GMENAC report recommended that the training of PA's should be maintained at the present level. At this rate we will have a near doubling of PA's by 1990. Can we simultaneously utilize the services of PA's while at the same time witnessing a physician glut without contributing to a medical surplus? Clearly, PA's cannot compete for the same primary care positions as physicians. PA's can no longer be viewed as being substitutive for physicians but must be looked upon as collaborative manpower. PA's, with the aid of federal funding, must move beyond traditional practice settings toward new clinical sites—to areas of practice that are collaborative and not competitive with a physician's practice. As Harmon and co-workers suggest, possible practice alternatives could be found in the areas of geriatric, occupational and correctional medicine.

With the graying of the population, there will be more elderly to care for, both in and out of nursing homes. Social health problems have increased the number of drug addiction and correctional programs. The growth of big business has opened up areas of practice within industrial medicine. The Veterans Administration is threatened by the fact that they will not be able to provide medical care for the doubling of the veterans population by the turn of the century. For PA's these areas all represent future employment possibilities that are collaborative and not competitive in areas where physicians choose to practice.

I have attempted to suggest one solution for PA's facing physician oversupply, but since health manpower problems are never simple, continued debate between PA's and physicians is needed as we approach 1990.

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Topics in Primary Care Medicine

Hyperventilation Syndrome: A Diagnosis Begging for Recognition

GREGORY J. MAGARIAN, MD; DEBORAH A. MIDDAUGH, MD, *and* DOUGLAS H. LINZ, MD, *Portland*

"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

—BERNARD LO, MD
STEPHEN J. McPHEE, MD
Series' Editors

Beginning with the American Civil War, military physicians seeing soldiers under the stress of combat have described a syndrome characterized by breathlessness, lightheadedness or dizziness, pronounced fatigue and exercise intolerance, numbness and paresthesias and chest pain. Rarely have organic diseases been found to account for the symptoms in such cases, yet despite reassurance, symptoms commonly persist for prolonged periods despite removal from the apparent stress setting. This syndrome has been given many names including irritable heart, soldier's heart, Da Costa's syndrome, effort syndrome, neurocirculatory asthenia and, more recently, hyperventilation syndrome.

Since the original descriptions in soldiers, it is now recognized that hyperventilation occurs in many persons under stresses of daily living. It is manifest not only in those overtly stressed, anxious and depressed but also in those who appear outwardly calm as they "bottle up" their feelings, often because of undeveloped or lack of acceptable emotional outlets. Physicians and lay persons alike readily recognize acute hyperventilatory attacks occurring under acute stress. However, chronic or recurrent hyperventilation problems often are unrecognized probably for a variety of reasons, including the frequent lack of obvious overbreathing, a tendency to focus on one or two complaints that alone are not particularly suggestive of hyperventilation, minimal discussion of the topic in medical school and cursory coverage in medical textbooks.

Physiology of Hyperventilation

Although precise delineation of the relationship between physiologic responses and symptoms of hyperventilation is lacking, an understanding of known physiologic mechanisms does provide insight (Table 1).

Hypocapnea and respiratory alkalosis develop rapidly upon onset of hyperventilation and can easily be maintained indefinitely, by nearly imperceptible hyperventilation, such as by taking an occasional deep breath while maintaining a normal respiratory rate. Without knowing this, physicians may directly observe the subtle, chronic form of hyperventilation without recognizing it or, upon considering the diagnosis, inappropriately reject it because the anticipated hyperventilatory respiratory pattern is not present.

Stress is often associated with a hyperadrenergic state that is known to provoke hyperventilatory responses in humans. Beta-blocking drugs may reduce not only stress levels but also ventilatory responses to catecholamine stimulation and have recently been shown to improve performance levels in stressful situations.

Respiratory alkalosis increases the avidity of oxygen binding to hemoglobin such that oxygen becomes less readily released to tissues (the Bohr effect). Hypophosphatemia develops rapidly and persists for the duration of respiratory alkalosis, probably related to intracellular shifts of phosphorus. With persistent hyperventilation, hypophosphatemia would impair generation of

Refer to: Magarian GJ, Middaugh DA, Linz DH: Hyperventilation syndrome: A diagnosis begging for recognition (Topics in Primary Care Medicine). West J Med 1983 May; 138:733-736.

From Ambulatory Care and Medical Services, Veterans Administration Medical Center, and the Division of General Medicine, Department of Medicine, Oregon Health Sciences University, Portland.

Supported in part by HEW grant No. 1-028-PE10051-02.

Reprint requests to Gregory J. Magarian, MD, Ambulatory Care Service (11C), Veterans Administration Medical Center, Portland, OR 97207.

TABLE 1.—*Physiologic Responses Associated With Hyperventilation*

Hypocapnic, respiratory alkalosis
Hyperadrenergic state
Increased oxygen binding to hemoglobin (Bohr effect)
Hypophosphatemia
Initial vasodilatory, later vasoconstrictive cardiovascular responses
Reduced cerebral perfusion
Possible coronary vasospasm

TABLE 2.—*Signs and Symptoms of Hyperventilation Syndrome*

General
Weakness, fatigue, sleep disturbances, blurred vision
Psychiatric
Anxiety, depression, phobias, feeling far away, sensations of unreality
Neurologic
Paresthesias in extremities or periorally, lightheadedness, dizziness, disorientation, impaired thinking, seizures, syncope, headaches
Cardiologic
Palpitations, chest pain
Respiratory
Dyspnea often without provocation characterized as being unable to take a satisfying deep inspiration, exaggerated thoracic breathing, sighing, yawning
Gastrointestinal
Dry mouth, bloating, belching, flatulence
Muscular
Cramping, spasm, musculoskeletal chest wall pain (chest wall syndrome)

2,3-diphosphoglycerate (2,3-DPG), further reducing oxygen availability for tissue utilization.

It is estimated that a 2 percent reduction in cerebral blood flow occurs for every decline of 1 mm of mercury in arterial carbon dioxide tension. This, along with the Bohr effect, leads to reduced cerebral oxygenation. Cerebral hypoxia, however, produces a vasodilatory response that may compensate for the initial reduction in cerebral perfusion.

Cardiovascular responses are variable and seem to be in large part related to the duration of hyperventilation. The initial response is a reduction in systemic vascular resistance and blood pressure with an increase in heart rate and cardiac output. Within four to seven minutes of sustained hyperventilation, however, this response diminishes or disappears.

Finally, several investigators have shown coronary vasoconstriction induced by hyperventilation in some patients with Prinzmetal's angina and others with fixed coronary occlusive disease.

Pathogenesis

How does the hyperventilation syndrome develop? Although hyperventilation may have organic or physiologic causes, the syndrome of hyperventilation is usually associated with emotional triggers and thoracic breathing tendency. Indeed, many persons who are anxiety-laden, stressed or depressed have hyperventilatory breathing patterns and complain of their inability to obtain satisfying deep breaths. Anxiety, anger and

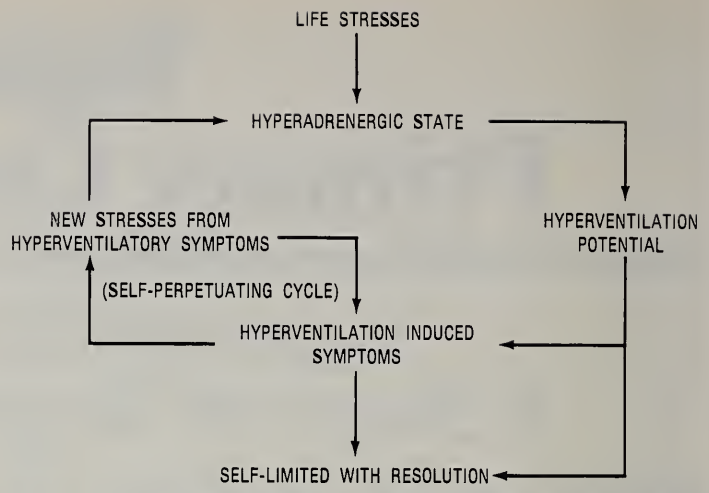

Figure 1.—Self-perpetuation theory of hyperventilation syndrome.

other emotions produce increases in both rate and depth of respirations probably mediated by a hyperadrenergic state. Once hyperventilation is initiated, persisting stresses of everyday living or the stresses of new bothersome symptoms from hyperventilation create the potential for a self-perpetuating cycle of chronic hyperventilation (Figure 1).

Persons who hyperventilate more commonly exhibit obsessional behavior, excessive body consciousness, phobias, feelings of inadequacy and maladjustments in many stages of life. Lum believes that an exaggerated tendency to breathe using thoracic musculature is an important factor allowing for the development and, once developed, the persistence of the hyperventilation syndrome.

Symptoms and Signs of Hyperventilation Syndrome

Among the most difficult and frustrating patients for physicians are those with multiple complaints involving many organ systems who, despite seeing numerous physicians, fail to obtain a satisfactory explanation or relief from their symptoms. They often have a "positive review of systems." After numerous physicians have been seen and multiple diagnostic tests have been done, which have excluded organic disorders, such patients are often dismissed as having nothing wrong with them or having a severe neurosis, anxiety, depression, hypochondriasis or hysteria, despite the persistence of symptoms that may be disabling in their work and other aspects of everyday living. Unfortunately, this scenario continues to be a common occurrence and is the frequent setting in which the hyperventilation syndrome is recognized, months or years after its onset. Previous studies have shown that 5 percent to 10 percent of patients seeking care from primary care physicians have at least some complaints related to hyperventilation.

The hyperventilation syndrome may be associated with a myriad of symptoms (Table 2), affecting both men and women equally. The most frequent complaints for which medical attention is sought are lightheaded-

ness or dizziness, dyspnea and chest pain. Substantial weakness, exercise intolerance, fatigue and peripheral or perioral numbness and tingling, occurring in isolation or in concert with other hyperventilatory symptoms, are almost always present. Many patients have multiple other complaints. When symptoms are taken in isolation, the syndrome is often not considered. However, when taken together, the entire symptom complex often makes the diagnosis rather obvious.

The dizziness of hyperventilation may be described as lightheadedness or an unsteady, giddy feeling, similar to drunkenness or vertigo. In one review of 104 patients who presented to a specialty clinic for the evaluation of dizziness, 23 percent had hyperventilation as the sole or prominent contributing factor. There may also be some degree of disorientation and mental impairment.

Breathlessness is a common complaint and is usually described as the inability to inhale a satisfyingly deep breath. It may be manifested by periodic, predominantly thoracic deep breaths, sighing and yawning. Sighing dyspnea is not a manifestation of cardiac failure. Although the hyperventilation syndrome rarely is associated with an obvious increase in respiratory rate, astute observers usually will note an increase in thoracic respiratory efforts. Paradoxically, whereas many people take deep breaths in an effort to relax, they may be provoking the very state they wish to avoid. The dyspnea of the syndrome may arise from fatigued respiratory muscles, overworked from chronic, excessive respiratory efforts. Since this type of dyspnea rarely occurs in the absence of other related symptoms, it is important that other manifestations of the hyperventilation syndrome be sought in all cases of otherwise unexplained dyspnea.

Gastrointestinal manifestations include dry mouth, bloating, belching and flatulence, related to aerophagia associated with overbreathing. Depression with attendant anorexia and weight loss may mimic systemic disease.

Cardiovascular symptoms of the syndrome are primarily palpitations and chest pain, which may mimic angina. Continuous ambulatory electrocardiographic monitoring of hyperventilators has shown frequent sinus tachycardia and supraventricular arrhythmias, even during sleep. Hyperventilatory symptoms without apparent provocation may occur during these times.

The chest pain of hyperventilation is variably described. It may be sharp and stabbing, thought to be related to pressure on the diaphragm from gastric distention or diaphragmatic hypertonicity related to a generalized hypertonic muscular contractile state. Other types of chest pain have features that may strongly suggest angina including location and radiation patterns. The pain may be described as dull, gnawing, burning or constricting and localized to the precordial or retrosternal area but is often rather diffuse and of greater duration than is typical of angina pectoris. It is not predictably associated with events that usually provoke angina, frequently occurring at rest or after exertion, and is not reliably relieved by nitroglycerin. Occasionally, "pseudoischemic" electrocardiographic patterns may be seen in patients with chest pain from hyperventilation. It currently remains uncertain whether hyperventilation-induced coronary vasospasm and myocardial ischemia contribute to the chest pain associated with the hyperventilation syndrome. Unfortunately, a diagnosis of noncardiac chest pain, while initially gratifying, usually does not result in a significant reduction in outpatient clinic or emergency room visits as symptoms often persist. Therefore, in evaluating chest pain, the historical data base should include questions directed toward the possibility of hyperventilation lest the etiologic basis of the chest pain be dismissed as noncardiac, yet unrecognized as hyperventilatory.

Other symptoms of hyperventilation are usually present but rarely offered voluntarily. Apart from other disorders the patient may have, the physical examination is often normal. Patients often do not appear overtly anxious though they are frequently depressed. Obvious hyperventilation is usually lacking although occasional deep breaths, sighing or yawning and palpable chest wall tenderness may be noted. The diagnosis of chest wall syndrome requires exclusion of the hyperventilation syndrome which may be its basis.

It is critical to recognize that the presence of the syndrome does not exclude the presence of an organic disease. In fact, reaction to the symptoms of an organic disease may be a prime factor provoking hyperventilation.

Management of Hyperventilation Syndrome

As many patients with the syndrome have had symptoms for months or years and have seen other physicians without appreciating the cause of their symptoms, it is important that the patient be confronted with the cause-and-effect relationship between hyperventilation and their symptoms. A hyperventilatory trial is crucial for therapeutic success. This can be accomplished by having the patient breathe deeply at a rate of 30 to 40 times per minute. Most patients with the hyperventilation syndrome will recognize at least some of their symptoms within several minutes and often in seconds. This recognition and subsequent explanation of hyperventilation greatly enhances the potential for improvement. An explanation and reassurance without the patient actually experiencing the cause-and-effect relationship of overbreathing at the time is often without therapeutic benefit.

After provocation of symptoms during a hyperventilatory trial, breathing into a lunch bag-sized brown paper bag will result in resolution of those symptoms that are directly related to hypocapnea. Dyspnea and chest pain, however, may persist in that they are not caused by hypocapnea, but more likely by the excessive use of thoracic musculature.

Because many patients have experienced substantial adverse effects on their employment and social interactions it is beneficial for a spouse or a friend to be present during a hyperventilation trial. Family and

friends may be highly skeptical that something as simple as overbreathing can be having such devastating effects on the patient and indirectly upon them as well. Convincing both the patient and others provides support for the patient as he or she attempts to regain control.

Although some believe bag rebreathing is of little value, we have found it to be useful, allowing patients an escape from symptoms. Initially, we encourage patients to attempt bag rebreathing, relax and get away from the situation that may have triggered the response. As a result, patients appreciate a newfound control. This greatly reduces the anxiety and stress that fuel the hyperventilation cycle.

Long-term control may be achieved by relaxation therapy and retraining patients to become diaphragmatic rather than thoracic breathers. Referral to behavior modification experts may be of value in particularly difficult patients with long-standing symptoms. In anxious and depressed persons with chronic hyperventilation we have rarely seen substantial benefit from the use of anxiolytic or antidepressant medications when the hyperventilatory component was unrecognized or being inadequately addressed. In conjunction with therapeutic measures directed toward the hyperventilatory tendency these drugs may be of additional benefit though we often find them unnecessary.

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Medical Practice Questions

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Photoradiation Therapy

QUESTION:

Is laser therapy (photoradiation therapy) for the treatment of malignancies considered acceptable medical practice? If so, is the addition of augmentative drugs, such as hematoporphyrin derivative (HPD), equally acceptable?

Is laser therapy in current use for specific types of malignancies?

OPINION:

In the opinion of the Scientific Advisory Panels on General Surgery, Internal Medicine, Obstetrics and Gynecology, and Radiology, laser therapy for certain types of preinvasive malignant conditions is established medical practice. It is accepted treatment for superficial malignant or premalignant lesions. The best experience seems to have been in the oral cavity, the larynx, the tracheobronchial tree and in the female genital tract (vulva, vagina and cervix). The place of laser therapy in the treatment of invasive primary tumors remains investigational.

The specific use of laser therapy following photosensitization of certain lesions with hematoporphyrin derivative (HPD) is investigational and should be conducted only under research protocol. The application of this technique, which requires training not yet available to the average surgeon, must await larger clinical trials to assess efficacy, better standardization of light and HPD doses, and the standardization of delivery systems and light sources. Photoradiation procedures are now limited to certain large centers where research studies are ongoing.

Though early reports have been promising, the proper role of laser photoradiation therapy in the treatment of cancer remains to be defined.

Health Care Delivery

Patterns of Antibiotic Use in a Busy Metropolitan Emergency Room:

Analysis of Efficacy and Cost-Appropriateness

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Antibiotics account for 15 percent to 20 percent of all new and refill prescriptions issued in ambulatory community practice. Antibiotic-prescribing practices in our emergency room for common outpatient infections—pharyngitis, bronchitis, sinusitis, otitis media, cellulitis, cutaneous abscesses and pneumonia—were evaluated. Antibiotic selection was compared with recommendations representing current standards for care, and the cost of each was approximated. Antibiotic agents were judged to be overused in patients with pharyngitis, bronchitis and cutaneous abscesses. Patients who had acute sinusitis and otitis media often did not receive antibiotics or received an antibiotic not active against Hemophilus influenzae. *A simple audit of antimicrobial drug usage for common outpatient infections proved to be a cost-effective way to identify excessive or inappropriate drug use. This approach could be used for evaluating the use of other drugs, and the results of these evaluations could serve to focus continuing educational programs.*

Antibiotics are among the most commonly prescribed classes of drugs. They account for 15 percent to 20 percent of all new and refill prescriptions issued in ambulatory community practice,[1] whereas about 30 percent of patients in hospital receive antibiotics whether they are admitted to community[2] or to university hospitals.[3,4] Evaluation of appropriateness of antibiotic use has focused primarily on patients admitted to hospital. In studies of inpatients, there has been little difference between community hospitals, where 62 percent of patients receiving antibiotics failed to have definite evidence of infection,[2] and university hospitals, where 64 percent of total antibiotic therapy was judged as not indicated or inappropriately administered in terms of drug or dosage.[3] Unnecessary therapy, poor drug choice or misguided prophylaxis was cited in one study in which the rate of inappropriate antibiotic administration was 41 percent.[4]

The use of antibiotics for problems in ambulatory patients has not been as thoroughly analyzed, but United States marketing research data indicate that 95 percent of physicians issue one or more prescriptions to a patient diagnosed as having the "common cold" and almost 60 percent of the prescriptions are for antibiotics.[1] The potential consequences of such practices include not only unnecessary risk from drug reactions, sensitization to antibiotic agents that may be required later and overgrowth of a resistant strain, but also excessive and unnecessary cost.

In an attempt to evaluate antibiotic-prescribing practices in our emergency room and ascertain the cost of this treatment, we reviewed patterns of antibiotic usage for common outpatient infections. The charts of all patients treated by house staff and attending physicians in a metropolitan university-affiliated hospital emergency room who had a discharge diagnosis of pharyn-

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gitis, bronchitis, sinusitis, otitis media, cellulitis, cutaneous abscesses or pneumonia were reviewed. Actual antibiotic selection was compared with recommendations representing current standards for care, and the relative costs of each were determined.

Methods

Background

San Francisco General Hospital Medical Center is a 600-bed acute care public hospital that serves as a major teaching hospital for the University of California, San Francisco. The adult emergency area is used by about 200 patients a day in three different areas: medical, surgical and ambulatory drop-in. These areas are staffed by medical students and interns under the supervision of medical and surgical residents and attending physicians. All cases are evaluated by either a resident or an attending physician.

Data Collection

A computer system was used to retrieve charts of patients who had discharge diagnoses of pharyngitis, bronchitis, sinusitis, otitis media, cellulitis, cutaneous abscess or pneumonia from July 1, 1980, to November 30, 1980. A random sample of charts with each diagnosis was then evaluated for age, allergies, underlying illness, treatment and other pertinent information depending on the diagnosis—for example, whether or not a throat culture was done when there was a discharge diagnosis of pharyngitis. The basis of the discharge diagnosis was not evaluated.

Standard of Care Criteria

The following criteria for treatment of the specific infections were established by a review of the current medical literature. Penicillin is regarded as the therapy of choice for group A streptococcal pharyngitis. This treatment prevents acute rheumatic fever, parapharyngeal abscesses and suppurative adenitis, though it has little effect on the natural course of the illness.[5] It is difficult on clinical grounds to differentiate group A streptococcal pharyngitis from pharyngitis caused by viruses or *Mycoplasma pneumoniae,*[6] and because only 20 percent to 25 percent of cases of pharyngitis are caused by group A streptococci, it is recommended that results of a throat culture dictate whether or not antibiotics should be used.

The choice of an antibiotic for the ambulatory treatment of pneumonia should depend on the bacteria causing the infection. A proper Gram's stain of a carefully collected specimen of expectorated sputum is the most rapid method of predicting the bacteria causing the pneumonia.[7] Treatment with penicillin is a reasonable choice if a Gram's stain shows a predominance of Gram-positive lancet-shaped diplococci indicating *Streptococcus pneumoniae,* or ampicillin if a Gram's stain shows either a predominance of Gram-negative coccobacillary forms suggesting *Hemophilus influenzae* infection or a mixture of both forms. Erythromycin is active against *S pneumoniae,* which causes pneumonia in all age groups. It is also active against *M pneumoniae,* which frequently causes pneumonia in older children and young adults.[8] Thus, if a sputum specimen cannot be obtained in a patient with pneumonia who is younger than 40 years of age (in whom *H influenzae* pneumonia is rare), erythromycin treatment is a rational choice. In patients older than 40 years of age who have community-acquired pneumonia, the choice of an antibiotic, if sputum cannot be obtained for Gram's stain, is more difficult. Older studies of community-acquired pneumonia derived much of their data of bacterial cause from the results of sputum cultures.[9,10] Since these studies were carried out, sputum cultures have been shown to be an unreliable way of determining the bacterial cause of pulmonary infections.[11] Although *H influenzae* appears to be an agent more commonly causing pneumonia in older patients who have chronic bronchitis than previously appreciated,[12] its incidence in the general population has not been determined. Erythromycin is not consistently active against *H influenzae* in achievable serum concentrations. We cannot yet make a firm recommendation for the choice of an antibiotic in the outpatient management of community-acquired pneumonia in patients older than 40 years of age when sputum cannot be obtained for Gram's staining. Given the current state of knowledge and the low incidence of β-lactamase-producing *H influenzae* in our population (5 percent), ampicillin would probably be the appropriate choice.

A diagnosis of acute bronchitis is made when a patient presents with a cough and purulent sputum production, and no abnormalities are found on a chest roentgenogram. Patients who have a diagnosis of acute bronchitis and a history of chronic pulmonary disease —most of whom are older than 40 years of age— benefit from the use of antibiotics, but otherwise healthy people do not.[13] The presence of cough and purulent sputum and the amount of time away from work are similar in patients without a history of chronic pulmonary disease whether or not they are treated with antibiotics.

Acute sinusitis and otitis media in adults and children are caused by a variety of aerobic and anaerobic bacteria of which *S pneumoniae* and *H influenzae* are by far the most frequently found.[14,15] Therapy aimed at these two agents has been shown to be effective.[16] Ampicillin or amoxicillin trihydrate and trimethoprim-sulfamethoxazole in a penicillin-allergic patient reach serum concentrations that are active against most of these organisms and represent rational treatment for acute sinusitis or otitis media.

Surgical drainage of localized cutaneous abscesses is the treatment of choice and antibiotics are generally of little value in patients with normal host defenses.[17] Because *Staphylococcus aureus* is the most common cause of cutaneous abscesses, however, it would be important to choose an agent active against this organism when there is enough toxicity or associated cellulitis to warrant antibiotic administration.

The bacterial cause of cellulitis may not always be

TABLE 1.—*Evaluation of Therapy*

Diagnosis	*Number of Patients*	*Most Important Treatable Pathogens*	*Therapy of Choice*	*Percentage Treated Incorrectly**
Pharyngitis	50	Group A streptococci	Penicillin	50†
Ambulatory pneumonia	27	*Streptococcus pneumoniae* *Mycoplasma pneumoniae* *Hemophilus influenzae*	Penicillin,‡ ampicillin, erythromycin	0
Bronchitis	106	Mixed flora	Tetracycline, ampicillin, erythromycin	50§
Sinusitis	24	*S pneumoniae* *H influenzae*	Ampicillin, trimethoprim-sulfamethoxazole	79
Otitis media	26	*S pneumoniae* *H influenzae*	Ampicillin, trimethoprim-sufamethoxazole	88
Cutaneous abscesses	39	*Staphylococcus aureus*	Incision and drainage	49‖
Cellulitis	31	Streptococci *S aureus*	? Penicillin vs dicloxacillin	0

*Treated with antimicrobial agents that would not be expected to be effective against the major treatable pathogens.
†Treated before knowing results of throat culture.
‡Choice of antibiotic dependent on findings of Gram's stain.
§Antibiotic therapy indicated only in patients who have a history of chronic pulmonary disease.
‖Received antibiotics in addition to incision and drainage.

clear from physical examination of the involved area.[18,19] Although a well-marginated, raised, brightly erythematous area of infection usually represents infection caused by a group A streptococcus, *S aureus* has occasionally been implicated in similar-appearing lesions. A recent study of 20 children who had cellulitis found *S aureus* in cultures of eight wound aspirates.[20] It is therefore rational to treat cellulitis with an agent active against both *S aureus* and group A streptococci, especially when it involves the face where the consequences of inappropriate therapy might be devastating. However, the vast majority of cases of typical erysipelas of the extremities respond to penicillin or, in a penicillin-allergic patient, erythromycin. The presence of pus should dictate the administration of antistaphylococcal drugs such as dicloxacillin sodium or cloxacillin sodium.

Results

Patterns of Antimicrobial Drug Use

In all, 50 cases in which a discharge diagnosis of pharyngitis was made were evaluated (Table 1). Although 47 patients (94 percent) had a throat culture done initially for group A streptococci, half were treated with penicillin before culture results were obtained. These patients were told to call the hospital to find out the culture results and whether or not to discontinue therapy.

There were 27 cases of roentgenographically proved pneumonia in which ambulatory patients were treated. When a sputum Gram's stain showed Gram-positive diplococci in six patients, a presumptive diagnosis of pneumococcal pneumonia was made and the patients were given penicillin. Ampicillin was given to four patients when a sputum Gram's stain showed mixed flora. Erythromycin was used in all patients who could not produce sputum. (This pattern did not vary in the 11 patients older than 40 years of age for whom *M pneumoniae* is presumably not an important cause of pneumonia.)

Patients with a discharge diagnosis of bronchitis were treated the same whether they were young and healthy or had a history of either chronic bronchitis or obstructive pulmonary disease or both. Of 59 patients younger than 40 years of age, 50 (85 percent) received antibiotics, and of 47 older than 40 years of age, 40 (85 percent) received antibiotics. Therefore, at least 50 percent—and probably a much higher proportion—of patients received inappropriate and unnecessary treatment. The choice of an antibiotic was almost evenly divided among erythromycin, ampicillin and tetracycline.

Of 24 adults with a clinical diagnosis of acute sinusitis, only 13 (54 percent) received antibiotics. Penicillin was prescribed for three, erythromycin for four, ampicillin for five and tetracycline for one. Two of the four patients given erythromycin had a history of penicillin allergy.

Of 26 adults with acute otitis media, 16 (62 percent) received antibiotics. Ten received penicillin, two erythromycin and two ampicillin. Of the three patients with a history of penicillin allergy, two received erythromycin and one received trimethoprim-sulfamethoxazole.

Of 39 patients with cutaneous abscesses, 33 (85 percent) required surgical drainage. Oral antibiotics were also administered to 19 patients: eight received penicillin, nine dicloxacillin, one erythromycin and one cephalexin.

Of 31 patients with nonfacial cellulitis, 30 (97 percent) received antibiotics. Of these, 16 were treated with penicillin, 10 with dicloxacillin and 4 with erythromycin. All four patients who received erythromycin had a history of penicillin allergy.

Cost of Antimicrobial Drug Therapy

The cost of the different antimicrobial agents used is shown in Table 2. Note the considerable differences both among different antibiotics and different preparations of the same antibiotic. There was also a large

TABLE 2.—*Cost of Antimicrobial Drugs*

Antimicrobial Drug	*Number of Different Preparations Available*	*High**	*Low**	*Average Cost**	*Cost at SFGHMC†*
Ampicillin 250 mg	32	$10.00	$ 4.50	$ 6.42	$ 4.00
Ampicillin 500 mg	29	27.50	8.95	12.42	7.00
Erythromycin 250 mg	31	14.95	6.10	8.51	4.00
Erythromycin 500 mg	13	25.90	12.95	17.19	...
Penicillin V 250 mg	10	4.75	2.30	3.37	2.00
Penicillin V 500 mg	6	9.50	4.50	6.59	4.00
Dicloxacillin sodium 250 mg	3	54.86	26.90	39.26	9.00
Dicloxacillin sodium 500 mg	2	85.84	46.40	66.12	18.00
Sulfamethoxazole-trimethroprim 160 mg/800 mg	2	38.04	37.25	37.65	5.00
Tetracycline 250 mg	26	4.00	1.95	2.78	2.00
Tetracycline 500 mg	25	6.04	3.60	4.64	6.00

*Cost of 100 tablets to the pharmacy, based on *American Druggist Blue Book,* 1981-1982 edition.

†Cost of 100 tablets to the San Francisco General Hospital Medical Center Pharmacy, where antibiotics are purchased on a bid system.

variation in cost depending on how the drugs are purchased. At large institutions, antibiotics are usually purchased directly from a manufacturer using a bid system, which can result in large savings. For smaller institutions and individual pharmacies, the cost is usually greater; antibiotics are sometimes purchased through a wholesaler—who adds 15 percent to 20 percent—and not directly from a manufacturer.

Discussion

This study reveals surprising inconsistencies in patterns of antibiotic use for commonly encountered outpatient problems. In many cases patients were administered antibiotics unnecessarily or were given antibiotics that were not active against the major pathogens causing their infectious disease. Unnecessary use of antibiotics is expensive and potentially dangerous. Antibiotics may alter a patient's endogenous flora and favor the development or emergence of resistant strains or the acquisition of new strains with multiple antimicrobial resistance. Antibiotic use may also result in allergic or other serious side effects.

Half of our patients who had pharyngitis were treated with penicillin before throat culture results were available. A rational and time-saving approach is to write a prescription for penicillin, tell the patient why it is necessary to take the drug if his or her infection is caused by group A streptococci and have the patient call the next day for results. If the culture is positive, the patient should have the prescription filled and take the antibiotic. This approach minimizes unnecessary drug exposure and expense.

Pneumonia was treated with penicillin if a Gram's stain showed a predominance of Gram-positive diplococci indicating *S pneumoniae,* ampicillin if the Gram-stained flora were mixed, raising the possibility of either *S pneumoniae* or *H influenzae* infection, and erythromycin if no sputum could be obtained. Based on our evaluation of available data, this appears to be a rational and safe approach to antibiotic treatment of pneumonia in outpatients, though ampicillin would also be a good choice for patients older than 40 years of age when sputum cannot be obtained for Gram's staining.

Essentially all patients who had a diagnosis of acute bronchitis, including 85 percent of patients younger than 40 years, received antibiotics. About half of these patients were healthy and had no smoking history. Because healthy persons with cough and purulent sputum production do not benefit from antibiotic administration, such therapy in these cases must be judged as unwarranted.

In our series only 21 percent of patients who had acute sinusitis received an antibiotic active against both *H influenzae* and *S pneumoniae,* whereas 46 percent received no antibiotic. The bacterial organisms most frequently found in adults with acute otitis media are also *S pneumoniae* and *H influenzae;* yet only 12 percent of the patients in whom this diagnosis was made received ampicillin or trimethoprim-sulfamethoxazole, agents active against these organisms; 38 percent received no antibiotic.

Antibiotic treatment of localized cutaneous abscesses was also excessive. Of our patients with localized abscesses, 85 percent were treated with surgical drainage, but 49 percent also received antibiotics, which in patients with normal host defenses is usually unnecessary. Because *S aureus* is frequently found in abscesses, it would seem logical to choose an agent active against this organism if treatment with an antibiotic is considered necessary. Only 58 percent of the antibiotic regimens prescribed, however, included such an agent.

Treatment of nonfacial cellulitis reflected the indecision about the causative role of *S aureus* mirroring the different recommendations in standard infectious disease and dermatologic textbooks.[18,19] In all, 47 percent of patients were treated with regimens active against this organism, whereas the remainder received only penicillin, which was presumably prescribed for *Streptococcus pyogenes.*

Recently the rapidly rising cost of health care has begun to be scrutinized. During the 1970s, national

health expenditures more than doubled, with an average annual increase of 12.6 percent. During the past two decades, national health care expenditures increased from 4.5 percent of the Gross National Product in 1960 to 9.1 percent in 1978.[21] A large proportion of health care funds is spent for medicine, both inside and outside the hospital, and antibiotics comprise the single largest drug expense item, accounting for 33 percent of the national expenditure for drugs.[22]

Our study identified several potential areas in which antibiotic use could be modified to minimize the use of unnecessary antibiotics and health care costs. Antibiotics were overused in patients who had pharyngitis, bronchitis and cutaneous abscesses. In our hospital, of 30 patients per month seen in the emergency room with cutaneous abscesses, approximately a third were given an inappropriate course of dicloxacillin. Because each ten-day course of dicloxacillin (250 mg four times a day) costs $7.20, this can result in a potential savings per month for ten patients of $72. The average cost to a pharmacy for a ten-day course of the same dosage of dicloxacillin is $15.70, or $18.05 to $18.89 if purchased from a wholesaler. The actual cost to a patient or health insurer is higher because of the pharmacy's fee for filling the prescription. About 60 patients with pharyngitis are seen in our emergency room per month. Half of the patients are treated with penicillin before throat culture results are available. Because only 20 percent of throat cultures are positive, 24 patients fill an unnecessary prescription for penicillin (250 mg four times a day) that costs $4.40 for a ten-day supply, a potential savings of $105.60 per month. Half of the 40 patients per month diagnosed as having bronchitis received an unnecessary course of antibiotics. If all were given ampicillin (500 mg four times a day), this would result in a potential savings of $128 a month in our hospital; the costs of erythromycin and tetracycline would be similar. All of these figures, of course, are without a pharmacy's or a wholesaler's additional fee.

In addition, in situations in which different antibiotics are equally efficacious, it seems reasonable to prescribe the least expensive antibiotic. Given the twofold to threefold differences in cost among pharmacies between tetracycline and ampicillin or erythromyin, the potential savings are considerable when choosing an antibiotic to treat a patient who has chronic pulmonary disease and acute bronchitis. A similar point can be made regarding the choice of ampicillin versus trimethoprim-sulfamethoxazole for the treatment of either sinusitis or otitis media. Penicillin V is 12 times less expensive than dicloxacillin, and thus a study to determine the relative importance of *S pyogenes* versus *S aureus* as the causative agent in cellulitis in adults could be justified on a cost basis alone.

The information presented herein shows the need for continuing surveillance of antibiotic-prescribing practices. This study and others[4,23] point to the need to educate physicians further about the basic principles of clinical infectious diseases, particularly antibiotic selection, based on what is known of the bacterial causes of different conditions. When appropriate, the cost of different drug regimens should be taken into consideration in prescribing antibiotics. Correcting the over-prescribing of antibiotics for commonly encountered outpatient infections could result in considerable savings not only to patients but also to health insurers or society when the government is the insurer.

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Medical Schools of the West

Loma Linda University School of Medicine

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Students were first accepted into medical school in Loma Linda in 1909 (see Figure 1) and the first class was graduated in 1914. Graduation has continued each year without interruption since that time. The forerunner of Loma Linda University School of Medicine was the American Medical Missionary College at Battle Creek, Michigan, and many of the early faculty of Loma Linda were graduates of that school. The medical school was called the College of Medical Evangelists until 1961, when the name was changed to Loma Linda University.

In 1913 clinical teaching was begun in Los Angeles. A clinic was started in Boyle Heights, from which the White Memorial Clinic and Hospital developed. This institution, owned and operated by the school itself, became a primary teaching unit. In 1914 students began to receive instruction at the Los Angeles County Hospital and clinical instruction was continued there until 1966.

In the 1940s and, especially, in the 1950s, considerable discussion arose relating to the advisability of consolidating the various facilities of the school on one campus. For pragmatic and financial reasons it seemed simplest to move the basic science aspects of the school to Los Angeles. On the other hand, it was thought that the school's identity and thrust could best be maintained by centralizing everything in Loma Linda. After lengthy debate, the latter course was chosen. To assure the success of the move, the Board of Trustees voted to underwrite the building of a medical center and teaching facility of more than ½ million square feet. In addition, some financial help was given for clinical faculty who were asked to move to Loma Linda. The decision to move to Loma Linda was made in 1962, and by the summer of 1964 construction had actually begun on the medical center, which was completed in 1967 (see Figure 2). In 1963 an affiliation was worked out with the Riverside General Hospital which has continued to date.

Enrollment and Curriculum

The decade and a half since consolidation at Loma Linda paralleled a time of intense pressure by society to increase the number of physicians. Beginning with the class admitted in 1963 Loma Linda had decreased enrollment so as to accommodate the move to Loma Linda, where facilities were more limited than those available in Los Angeles. As the hospital and affiliations became operative, however, enrollment was gradually increased. With progressive financial incentives by the federal government further increases were made. These first federal incentives were followed by a program of the state of California that offered capitation to the three private medical schools in the state if they would further increase enrollment. This rather large capitation offer was to be without precondition as to how the money would be spent by the medical schools. Unfortunately, after an increased number of students were accepted, the program was ruled unconstitutional, and Loma Linda did not receive any of the expected funds. The additional students accepted in anticipation, however, did establish the base for later federal capitation incentives.

In 1968 a curriculum was introduced integrating the basic sciences and clinical rotations, thereby giving students early clinical experience. Under this program the entire senior year was elective; but although philosophically the curriculum seemed to be ideal, it had some pragmatic drawbacks. First, because the integrated blocks were handled by committees, responsibility was not easily assigned. It was found far more successful to hold a department responsible through its departmental head than to deal with an interdisciplinary committee or its chairman. Although the loose structure of the fourth or elective year did fit well for some ambitious, well-motivated students, it had two serious problems:

1. Students were encouraged to take elective experi-

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ence that would be of interest and benefit to the student but which would not necessarily contribute to general and clinical education.

2. The evaluation mechanism was less standardized, and it was found that some students probably suffered for the lack of structure and guidance.

After experience with three classes this interdisciplinary approach was abandoned and the curriculum changed to a classic basic science/clinical subject format. However, to meet the pressure of an increased enrollment a program was developed in which two classes were accepted each year, one in the spring and another of equal size in the fall. All basic science courses were thus taught twice each year. This had the advantage of maximal use of physical facilities. It also allowed for more flexibility in the medical school program in that some students could travel at a slower pace, and those choosing a faster pace could graduate in as little as 39 months. Also, the necessity of repeating subjects would not entail the loss of an entire year. The following disadvantages were noted:

- Fatigue of students and faculty, resulting from lack of breaks.
- Pressure on teaching faculty counterproductive to research efforts.
- Graduations twice each year (approximately June 1 and December 1) and increasing difficulty in finding postgraduate slots for the December group. This became a serious problem as the number of available postgraduate slots dwindled in comparison to the number of US graduates. The school continued this program for six years, or 12 classes.

As the problems mentioned above developed, the curriculum committee on the basis of an in-depth study recommended a return to the four-year curriculum with one class each year. In this program the basic science courses were distinct and occupied much of the first two years.

More recently a section in community medicine has been developed and has been expanded. Physical diagnosis is taught in both freshman and sophomore years. During the junior clerkships time has been allotted

Figure 1.—The original main building in Loma Linda when the property was purchased in 1905.

for exposure to family practice. Both family practice clinics and private physician offices are being utilized.

Funding and Facilities

Due to the consolidation of the medical school on the Loma Linda campus it was necessary to develop a medical center in which the clientele were private patients of physicians. This led to development of a clinical faculty centered about the care of patients, particularly in a tertiary medical center environment. The time of the move of the school was also the time of increased federal support. During these years the school of medicine did receive considerable federal funds in the form of capitation grants, as well as other kinds of grants. However, the school found itself faced with a number of restrictions connected with the capitation grants related to public law 94-484 (The Kennedy-Rogers Bill), which was passed in 1976. In early 1978 these problems were carefully considered by both the faculty and the Board of Trustees. The decision was made to decline further federal support of this nature. In doing this, the faculty did realize the vulnerability of the school because of the loss of such funds, and this realization helped accelerate the completion of a faculty practice structure whereby the clinical departments or sections were organized into practice groups or corporations—under a steering corporation in which the University Vice President for Medical Affairs and the Dean of the University School of Medicine are President and Vice President respectively.

The practice groups not only serve as the employing structure for the full-time clinical faculty but give support for research and teaching. At present this faculty practice structure makes a very important contribution to the financial soundness of the medical school.

The decision to forego capitation had also one other salutary effect. The faculty believed that the number of students had become too large for adequate clinical instruction. Hence, because the school was no longer under a minimum enrollment mandate, a decision was made to decrease enrollment from a high of 166 students per year to 140. Four successive classes now have

Figure 2.—The medical center, completed in 1967.

been admitted with a smaller enrollment. The present number is 140.

The university hospital with a 546 bed unit was completed in 1967. The Jerry L. Pettis-Memorial Veterans Medical Center hospital was completed and opened in 1977. This modern 500 bed unit is integrated into the undergraduate and postgraduate teaching of the medical school. A new basic science building is under construction, a project of the medical school alumni. It is due to be completed this year.

A strong effort is being made to encourage the spirit of inquiry among students and faculty. A number of scientists active in research have been recruited. At present there are centers of excellence in such fields as neurobiology, perinatal physiology, coagulation and red cell biophysics; recently added is a large team working in bone metabolism.

Summary

The past decade and a half has been a time of consolidation and unification of the school on the campus at Loma Linda. At the time the decision was made to consolidate the school on the Loma Linda campus, there was considerable apprehension about whether the move to a rural area 60 miles east of Los Angeles would be successful. All now agree that it was opportune in time and place. The campus is spacious and the setting ideal. There is a community of students and faculty that allows for much closer interaction and contact than before. The close relationship with other health-related schools in a medical center makes for a closer working relationship; the setting has allowed the development of a team approach to patient care which emphasizes the caring and compassion that are in keeping with the basic goals and purpose of the school. The faculty-to-student ratio has been increased, and a preceptorship system has developed whereby faculty members become involved closely with specific students. In addition, the move to Loma Linda proved that there was a need for a tertiary care facility in this part of California, the "Inland Empire."

Along with other developments there has been increased interest in international aspects of medical practice. At present 160 of our alumni are in foreign countries, and during the past ten years the Loma Linda University heart team has been active in a service and educational program in Vietnam, Saudi Arabia and, more recently, in China. A number of other faculty members have been involved in medical education abroad, and a sizable number of students have been going to overseas mission hospitals for their three months senior elective experience. This widened experience has stimulated an interest and desire to serve the needy in deprived areas in distant lands as well as at home.

In the past three years there have been active MD/MS and MD/PhD programs, and the school is sponsoring a medical scientist training program in which selected students will receive training in molecular biology and research integrated with the training for an MD degree. The long-range goal is to develop research-oriented clinicians who as future faculty members can enrich the school's educational program—developing not only able clinicians but clinicians with an inquiring mind and with the desire to add to medical knowledge.

Information

Recommendations for Patients Traveling

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Traveling patients often rely on their personal physicians for advice about immunizations and the health hazards of traveling. Although public health departments frequently serve as Official Vaccination Centers, today's sophisticated travelers may also need detailed and personalized advice, prescriptions or special pretravel evaluations when about to embark on extensive travel to exotic parts of the world.[1] The emphasis of this article is on the needs of traveling patients going to areas of the world where food and sanitation may be a problem.

Medical advice to travelers can be separated into three phases: (1) the pretravel period, (2) the travel period and (3) the posttravel period (see Table 1).

Pretravel Period

Pretravel evaluation and immunizations may require up to six weeks, so potential travelers should be advised to see their physicians early.

As part of a pretravel evaluation, all patients should be interviewed regarding their general medical condition and their history of immunizations, medications, allergies, dietary restrictions and any need for limiting activity. Special note should be made of immunosuppressed patients because exposure to live virus vaccines may be contraindicated in such persons. These patients may also need advice regarding special precautions and contingency plans in case of serious illness during travel.

A business traveler going on a three-day business trip to Western Europe may only require updating of routine immunizations such as tetanus and diphtheria, and a medication to help with problems of jet lag. A vacationing family leaving for a sailboat trip around the Caribbean may need special consideration of their poliomyelitis immune status and a discussion of ciguatera fish poisoning. A tourist going to Mexico may want information on the latest prophylaxis and medications for traveler's diarrhea.

For patients going overseas on extended assignments (a year or longer) or for patients planning shorter trips but anticipating intimate contact with rural people and environments, especially in tropical or subtropical wilderness areas, a more complete evaluation should be considered. In addition to a physical examination, a leukocyte differential, a serum chemistry panel, a urine analysis, a skin test for tuberculosis or an x-ray study of the chest (or both), an electrocardiogram and a Pap test may be done. In addition, this kind of traveler-patient may often need certain vaccines recommended for those residing in a developing area of the world as well as *routine* and *required* immunizations.

Another type of patient who should receive special attention during travel preparation is a woman of childbearing age. Because live virus vaccines are generally contraindicated during pregnancy and for three months before pregnancy, plans for reproduction must be considered carefully during the pretravel visit. Iodide-based water purification methods, many of the common remedies for travel-related discomfort, certain of the non-live virus vaccines (especially cholera and typhoid vaccines where the risk is unknown) and medication for chloroquine-resistant forms of malaria may also present risks to a fetus.[2-6] Consideration of similar points is also appropriate for nursing mothers.[7]

Patients with a history of inflammatory bowel disease may desire special consultation before travel. All patients with serious allergies or chronic diseases or conditions should be urged to wear a medical identification bracelet during travel. All travelers should be reminded to carry a list of required medications, including both the generic and brand names, the dosages and the schedules of medication. If corrective lenses are required, a traveler should be reminded to carry an extra pair of eyeglasses and a prescription for the corrective lenses.

A traveler who allows at least six weeks before departure for immunizations that may be needed usually can be scheduled so that no more than two injections at separate sites need to be administered on a single day. However, if a traveling patient waits until the week before departure before considering recommended and required immunizations, multiple immunizations may be given, limited mainly by the availability of separate injection sites and the patient's tolerance of discomfort and side effects. Up to three live virus vaccines may be given to a patient on the same day at different sites without predictable loss of immunogenicity.[2] A live virus vaccine and one or more inactivated antigen vaccines can be given at separate sites at the same time. If time allows, it is generally wise to give immunizations that cause uncomfortable side effects on different days (for example, typhoid vaccine and plague vaccine).

Routine Immunizations

In the absence of specific contraindications, all travelers, regardless of destination, should be up to

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date on routine immunizations (Table 2). These include tetanus and diphtheria (Td); measles, mumps and rubella (MMR), and poliomyelitis vaccine (OPV or IPV).[2] Td, after the initial series of three vaccinations usually received in childhood, requires a booster every five to ten years for optimal protection.[8] The MMR primary series is generally administered during childhood, and boosters need not be given.[9-11] If the history of rubella vaccination is in doubt, rubella vaccination is recommended for women of childbearing age if they are certain that they are not pregnant and agree to delay pregnancy until at least three months after the vaccine is given.[11] As poliomyelitis is not uncommon in developing countries, immunization should be considered for previously unvaccinated adults, for incompletely immunized adults and even for adults who have previously completed a primary course of oral poliomyelitis vaccine (OPV) or inactivated vaccine (IPV) who are planning travel to such countries.[12,13]

TABLE 1.—*The Three Periods of Travel-Related Health Care and Precautions*

Pretravel Period
Vaccinations (allow 4 to 6 weeks)
Prophylactic measures as appropriate
Human immune globulin (protection against viral hepatitis, type A)
Chemoprophylaxis for malaria
Traveler's diarrhea
Assemble personal medical kit
Travel Period
Food and water precautions
Continue malaria chemoprophylaxis
Insect precautions
Measures for traveler's diarrhea
Posttravel Period
Continue malaria chemoprophylaxis for 6 weeks
Contact a physician if any of the following signs or symptoms develop: fevers, persistent diarrhea or abnormal bowel movements, abdominal pain, unusual skin lesions, any significant change in general health.

TABLE 2.—*Vaccinations*

For individuals engaging in international travel, routine and booster immunizations recommended by the immunization practices advisory committee (ACIP) for persons living in the United States should be up to date:

a. Diphtheria and tetanus (Td) (booster every 10 years)
b. Measles
c. Mumps
d. Rubella
e. Poliomyelitis (booster for increased risk of exposure, such as traveling to rural areas of developing countries)

Vaccinations that may be required by International Health Regulations (World Health Organization):

a. Cholera: certificate valid for *6 months* beginning 6 days after 1 injection of vaccine or on the date of revaccination if within 6 months of the first injection
b. Yellow fever: certificate valid for *10 years* beginning 10 days after primary vaccination or on the date of revaccination if within 10 years of first injection

Vaccinations and prophylaxis that may be specifically recommended to travelers, depending on destination, purpose and duration of travel:

a. Typhoid vaccine
b. Rabies vaccine (human diploid cell vaccine)
c. Plague vaccine
d. Meningococcal vaccine (serogroups A and C)
e. Immune globulin for hepatitis A (partial protection for 3 to 6 months depending on dose)

The choice of OPV or IPV for adults depends on the previous poliomyelitis immunization history, the nature and destinations of the planned travel and the length of time available for immunizations before departure. There is a rare risk of vaccine-associated paralysis following OPV in healthy recipients and their contacts. The risk of this complication is slightly higher in adults than in children, and substantially higher in patients with immune-deficiency diseases. However, in generally healthy travelers going to certain areas or countries where poliomyelitis is epidemic or endemic, the risk of disease from exposure to wild polioviruses may be greater than the rare risk of disease from the vaccine-associated viruses in OPV. OPV is usually preferred for primary immunization in children (generally, less than 18 years old) because it induces intestinal immunity and produces long-lasting immunity in more than 95 percent of recipients.

In previously immunized (IPV or OPV) adults, a supplementary dose of oral vaccine may be given before departure for an area where an increased risk of the disease exists, if there are no specific contraindications to this vaccine.

In previously unimmunized adult travelers going to high-risk areas, a complete primary series with four doses of IPV should be scheduled if time permits (12 months). If less time is available, up to three doses of IPV, each dose at least four weeks apart, should be given before departure. The remaining doses of vaccine can be given to the traveler after return, at the appropriate intervals to complete a primary IPV series if future travel to high-risk areas is anticipated. Additional doses of IPV may be given every five years for those adults completing primary IPV immunization, not wishing OPV and who will be at increased risk for polio exposure.[8,9]

Pneumococcal and influenza vaccine indications are probably no different for travelers than for other patients.[2]

Required Immunizations

Some countries may require proof of vaccination against certain diseases as a condition of entry according to International Health Regulations (Table 2).[2] These vaccinations, when required, must be recorded and validated by the stamp of an Official Vaccination Center in the yellow booklet *Certificates of Health for International Travel,* available at Official Vaccination Centers. Other immunizations and health information also should be noted in the booklet, and the document

carried in a safe place, usually with the traveler's passport.

Traditionally, smallpox, cholera and yellow fever were the diseases subject to International Health Regulations. However, the last endemic case of smallpox occurred in Somalia in 1977 and an active surveillance program conducted by the World Health Organization has found no additional documented cases of smallpox in the subsequent years. In 1981 the World Health Organization amended the regulations to remove smallpox from the diseases subject to the regulations effective January 1, 1982. All countries have agreed to the new recommendation except for the north-central African country of Chad.[14]

Due to administrative and communication difficulties, however, some embassies and consulates, travel agents and even staff at points of entry to a country may advise a traveler that a smallpox vaccination certificate is still required. If a traveler anticipates travel to Chad or any other area where a request for a smallpox vaccination certificate may become an issue, the traveler's physician may provide a written statement, preferably on letterhead stationery, that vaccination is contraindicated for health reasons. At present, smallpox vaccine generally is contraindicated even for patients in good health because of the significant risk of complication to vaccinees and their contacts.[2,14]

Information regarding vaccination requirements listed country by country may be found in *Health Information for International Travel,* published every year by the Centers for Disease Control.[2]

The cholera vaccine does not elicit a high degree of immunoprotection even when the full primary series of two injections at least one week apart is given. However, many countries in areas where cholera is endemic or epidemic do require proof of vaccination. A single dose of vaccine will satisfy International Health Regulations. The full primary series is sometimes recommended for people who will live and work in highly endemic areas and for people with underlying gastrointestinal conditions such as a gastrectomy or chronic peptic ulcer disease.[15]

Yellow fever is endemic in equatorial regions of South America and Africa. The yellow fever vaccine is often required for travelers going to those countries where the disease is endemic and also for entry into nonendemic areas when the traveler has recently visited an endemic area. This is a live virus vaccine which requires renewal every ten years. Yellow fever vaccine should not be given to immunosuppressed patients but, according to guidelines from the Centers for Disease Control, it may be considered for pregnant women if travel to an endemic area is *unavoidable*. The vaccine is prepared in eggs and may cause allergic reactions in sensitive persons.[16,17]

Optional Vaccinations

Vaccinations that are not required but that should be considered for certain travelers include typhoid, rabies, plague and meningococcal vaccines.

Typhoid vaccine should be recommended to travelers going to developing areas of the world where sanitation may be a problem. It has been shown to be 70 percent to 90 percent effective in preventing typhoid fever after a primary series of two injections four weeks apart, followed by a booster every three years. This vaccine contains *Salmonella typhi* antigens and may result in a febrile reaction, an influenza-like illness, and local discomfort for a period of one or two days following each injection.[18]

Although still relatively expensive, the new human diploid cell rabies vaccine appears to be highly effective in inducing a protective antibody response and should be recommended to travelers who anticipate close contact with wild or domestic animals in foreign countries. This would include veterinarians, certain laboratory workers, field biologists and children likely to play with animals. Three injections over a one-month period are required. The need for post-bite therapy is not eliminated by this vaccine, but it probably provides initial protection in case of delay in reaching medical attention and also simplifies the regimen then required. This vaccine is available through certain hospital pharmacies and state health departments.[19,20]

Plague vaccine is prepared from inactivated *Yersinia pestis*. It is recommended only for certain travelers to rural mountainous areas of South America, Asia and Africa, and for those whose work brings them into contact with wild rodents or rabbits in known areas of risk.[21]

A vaccine for meningococcal serogroups A and C has now been available for several years. It is not generally indicated for travelers but should be considered for medical personnel or others who may find themselves in an epidemic situation. The most recent epidemics have been noted in Brazil and the Sahel region of Africa.[22]

Typhus fever is endemic to mountainous Asia, the highlands of South America and certain parts of Africa, areas where conditions favor louse infestation. Selected travelers, particularly those who will stray from the usual routes taken by American travelers or who plan to work closely with the local population in endemic areas, should be educated about the risk of typhus and its appropriate treatment with tetracycline or chloramphenicol. Typhus vaccine is no longer produced in the United States or Canada.[23,24]

Hepatitis A Prophylaxis

As the viral hepatitis virus (type A) is a frequent water source contaminant and cause of infectious hepatitis in developing and tropical countries, human immune globulin should be given prophylactically to travelers who plan to visit these areas. When given in adequate dosages, immunoglobulin preparations provide considerable protection against this common form of hepatitis. For adults, a dose of 5 ml should be given intramuscularly every four to six months for optimal prophylaxis; a smaller dose may be used for short-term travel. Immune globulin generally should be adminis-

tered just before departure and two weeks following the last vaccine. Simultaneous administration with vaccines should be avoided because the immune globulin could reduce vaccine efficacy.[2]

Malaria Prophylaxis

Malaria is the world's most common infectious disease, and the risk of malaria exists in developing countries all over the world. Chemoprophylactic regimens have proved to be very effective when adhered to faithfully, but because of the emergence of chloroquine-resistant strains of *Plasmodium falciparum,* selection of the proper regimen has become more complicated in recent years. The Centers for Disease Control, their publications and local health authorities should be consulted for up-to-date information on the specific risk of malaria and appropriate chemoprophylaxis for a given area at any time.

In general, travelers to areas where only chloroquine-sensitive strains of malaria occur should be given chloroquine phosphate, 500 mg (adult dose) by mouth per week, beginning one week before arrival in, every week during travel in and for six weeks after return from a malarious area. In Southeast Asia (including Thailand and Indonesia), South America (including Colombia and countries bordering Colombia) and certain areas of Africa, chloroquine-resistant strains of *Plasmodium falciparum* are an increasing problem.[2] A combination of pyrimethamine, 25 mg, and sulfadoxine, 500 mg (adult dose), should be taken every week in addition to the weekly chloroquine dose by travelers to these places and should continue for six weeks after departure from the area.[25] The fixed-dose combination tablet is now available by prescription in the United States from pharmacies under the trade name Fansidar. Chloroquine phosphate and the pyrimethamine-sulfadoxine combination provide therapy against the erythrocytic phase of malarial infection, thus preventing expression of the clinical disease during prophylaxis with these agents. Some travelers, especially those with a history of heavy exposure to mosquitoes in malarious areas, should take primaquine phosphate, 26.3 mg each day for two weeks at the conclusion of posttravel weekly chloroquine therapy to eradicate the risk of posttravel malarial attacks from occult malaria *(Plasmodium vivax* or *Plasmodium ovale)* parasites in the liver (the extra-erythrocytic phase). Before prescribing primaquine, people at risk for hemolytic anemia during therapy due to glucose-6-phosphate dehydrogenase deficiency should be identified by laboratory testing, and alternative regimens considered.[25,26]

Traveler's Diarrhea Prophylaxis

Traveler's diarrhea, a well-known syndrome of sudden diarrhea occurring in international travelers, affects 30 percent to 60 percent of visitors to tropical and developing countries. Most cases are thought to be caused by enterotoxigenic *Escherichia coli,* although other agents including rotaviruses may be implicated. The watery diarrhea generally develops suddenly, may be accompanied by abdominal pain, cramps, nausea and vomiting and usually resolves spontaneously after three to four days of misery for the victim. Prevention, through strict avoidance of potentially contaminated food and water, is often successful but is often difficult. Two recently developed prophylactic regimens have been useful under certain circumstances and should be considered for selected patients.[1,3,27]

Bismuth subsalicylate (Pepto-Bismol) liquid, 60 ml taken by mouth four times a day, reduced the incidence of diarrhea from 61 percent to 23 percent in a three-week double-blind, controlled trial in students traveling to Mexico.[28] According to isolated reports of experienced travelers, a regimen of two Pepto-Bismol tablets three times a day, an easier form of Pepto-Bismol to transport, may also be effective and well-tolerated. There are limited data from a double-blind placebo-controlled trial suggesting that bismuth subsalicylate in other than liquid form is effective in prevention of traveler's diarrhea.[29]

Doxycycline, taken as an oral regimen, 100 mg per day, during travel may confer significant protection against diarrhea in tropical countries for periods up to three weeks.[30,31] Disadvantages of this regimen include the risks of vaginitis, photosensitivity and drug-related diarrhea as well as possible potential for infection with resistant organisms. This regimen is contraindicated in pregnant women and children less than 8 years of age.

The Traveler's Medical Kit

Finally, before departure travelers should be advised regarding medications and supplies to be carried in a personal medical kit. The items listed in Tables 3, 4 and 5 represent an extensive consolidation of potentially useful items. The individual traveler and his or

TABLE 3.—*Traveler's Personal Medical Kit—Prescription Items**

Meclizine (Antivert), 25 mg tablets, or scopolamine extended release percutaneous medication discs (Transderm V): for motion sickness
Chloroquine phosphate (Aralen), 500 mg tablets: for prevention of malaria
Pyrimethamine, 25 mg, plus sulfadoxine, 500 mg, tablets (Fansidar): for prevention of chloroquine-resistant *Plasmodium falciparum* malaria
Diphenoxylate hydrochloride (Lomotil), 2.5 mg tablets: to decrease diarrhea and cramping
Flurazepam (Dalmane), 15 mg capsules: for sleeping problems related to jet lag
Prochlorperazine (Compazine), 25 mg rectal suppositories: for severe nausea, vomiting
Erythromycin, 250 mg tablets: for skin or soft tissue infections
Tetracycline, 500 mg capsules, or trimethoprim/sulfamethoxazole (160/800 mg) tablets: for initial treatment of severe diarrhea when medical help is not available
Doxycycline (Vibramycin), 100 mg capsules: for prophylaxis of diarrhea in certain countries for travel of a limited duration

*The use of trade names in Tables 3, 4 and 5 is for identification purposes only, and does not constitute an endorsement. The contents of an individual traveler's medical kit should be selected from the extensive lists of products in Tables 3, 4 and 5, according to the nature, destinations and duration of the anticipated travel.

her physician should select the contents of a personal medical kit based on the circumstances and itinerary of the anticipated trip, and the traveler's level of medical sophistication.

Travel Period

Even appropriately vaccinated travelers need to pay attention to food and water in exotic or developing areas of the world. While following common-sense precautions, travelers need not miss out on local culinary delights. Travelers should be advised to select well-cooked foods, fruits that can be peeled by the traveler, and boiled liquids or carbonated bottled beverages. Salads, other raw or undercooked food, dairy products, shellfish and local untreated water should be avoided if there is any doubt about local sanitary conditions. In such areas, boiled water or tap water first made too hot to touch and then cooled, and iodine-based or water-filtration purification methods may be used when water of known purity is not available. While wine, beer and alcoholic beverages are generally safe, travelers should remember that ice-cubes could be a source of potential contamination.

TABLE 4.—*Traveler's Personal Medical Kit—Nonprescription Items*

Acetaminophen (Tylenol) or aspirin tablets: for general relief of minor aches and pains or headache
Antibiotic ointment (bacitracin or neosporin): topical antibiotic for minor cuts and abrasions
Bismuth subsalicylate (Pepto-Bismol), 8 oz liquid bottles (equivalent to 48 tablets): for symptomatic treatment, and for prevention of traveler's diarrhea
Decongestant and antihistamine capsules: for nasal congestion
Glucose and electrolyte powdered mix (Hydra-Lyte or similar product): to be mixed in safe water for fluid replacement and rehydration during severe diarrhea
0.5% Hydrocortisone cream (Cort-Aid): for topical relief of itching due to insect bites
Insect repellent liquid (Cutter's or Jungle Juice): for topical application
Insect repellent spray (Off): for use in unscreened rooms and other areas
5% Para-aminobenzoic acid lotion (PreSun 8): sun screen protection of skin
Povidone-iodine liquid (Betadine): cleansing of minor cuts and abrasions
Water purification straw (Pocket Purifier): for purification of unsanitary water, iodide-based, will produce purified water without the waiting period needed for the water purification tablets to work, for individual use.
Water purification tablets (Potable Aqua or Coughlan's): iodine-based tablets will kill microorganisms that chlorine-based tablets will not

TABLE 5.—*Traveler's Personal Medical Kit—General Supplies*

Bandages—Band-Aids, 2"x2" sterile gauze pads, roll of surgical tape
Case or box, metal or plastic—the smallest size that will accomodate contents of the medical kit
Dust mask—for use in dusty desert areas
Moleskin—blister protection for poorly-fitting shoes
Oral thermometer
Safety pins
Scissors—or sterile razor blade, or pen-knife, or "Swiss army knife"

TABLE 6.—*Measures for Traveler's Diarrhea*

World Health Organization Oral Rehydration Regimen:
Sodium chloride (table salt), 3.5 grams (½ tsp)
Sodium bicarbonate (baking soda), 2.5 grams (½ tsp)
Potassium chloride, 1.5 grams (¼ tsp)
Glucose 20 grams or sucrose 40 grams (glucose 2 tbsp or sucrose 2½ tbsp)
Dissolve in 1 liter of drinkable water. Drink 2 to 5 liters per day

Chemical Water Purification

In general, iodide-based methods of water purification are recommended over chlorine-based methods, because of the relative resistance of *Giardia* cysts to the latter. Iodide-based methods may include the use of iodine solutions,[2,32] iodine crystals,[33] iodide-containing tablets[34] or iodide-based ion exchange resin columns incorporated into "straws" (personal communication, Pocket Purifier of Washington, Seattle, 1982) or larger filtration devices. The "purification straw" is most convenient for obtaining a rapid drink of safe water. When larger quantities of purified water are needed, such as for brushing teeth or making beverages, the use of iodine solutions or tablets would be more practical, although a 30-minute wait is involved.

Traveler's Diarrhea Treatment

As symptomatic treatment for traveler's diarrhea, one study has shown a significant reduction in the number of unformed stools as well as relief from nausea and abdominal pain when 30 to 60 ml of bismuth subsalicylate liquid is taken every 30 minutes for a total of eight doses after the onset of symptoms.[35] For diarrhea of moderate to severe proportions (greater than five unformed stools per day) fluid and electrolyte replacement are of the utmost importance. The Centers for Disease Control formula of 8 oz of fruit juice containing a bit of honey and salt alternating with the same amount of carbonated or boiled water with ¼ teaspoon of baking soda, taken by mouth in volumes approximating fluid losses from diarrhea is easy to remember.[2] The World Health Organization formula or commercially available glucose and electrolyte powdered mixtures to be mixed in water of known purity are alternative regimens (Table 6).[27]

Persistent vomiting or diarrhea, bloody diarrhea, high fever, chills, inordinate abdominal discomfort and inability to maintain adequate hydration should be recognized as warning symptoms requiring prompt medical attention.[1] In cases of severe diarrhea when medical attention is not available, tetracycline therapy may be a useful adjunct to fluid and electrolyte replacement.[36,37] Trimethoprim/sulfamethoxazole (160 mg/800 mg) twice a day for five days has also been shown

to be efficacious in treating presumed traveler's diarrhea in adults.[38]

Although the use of agents that relieve diarrhea and cramps by their antimotility activity (Lomotil, Loperamide) are contraindicated in diarrhea accompanied by the warning symptoms listed above and may actually aggravate diarrhea and systemic complications caused by amebiasis, shigellosis and ulcerative colitis, the use of antimotility agents for a limited time in cases of watery traveler's diarrhea and cramps may be helpful to a stricken traveler who must leave his or her hotel room to make tour connections. If antimotility medications are used, the patient should be reminded to continue to pay attention to adequate fluid replacement measures for presumed intestinal losses.

Protection From Insects

World travelers should be reminded that in addition to malaria, other diseases (such as yellow fever, dengue, filariasis, leishmaniasis, trypanosomiasis and cutaneous myiasis) are carried by insect vectors. Adequate insect protection in the form of light-colored clothing that covers arms and legs, insect repellents, use of mosquito netting while sleeping in unscreened rooms and avoiding scented cosmetics may be especially recommended for rural tropical areas. In addition, malaria chemoprophylaxis must be taken faithfully during travel.

Other environmental hazards to be avoided include excessive sun exposure in tropical areas and swimming or bathing in fresh water lakes, rivers or streams in areas endemic for schistosomiasis (a risk in parts of the Caribbean, South America, Africa, the Middle East and Asia).

Posttravel Period

In spite of an absence of symptoms in a returning traveler, it must be remembered that malaria chemoprophylaxis should be continued for six weeks after departure from an endemic area, and the need for primaquine therapy considered.[25]

Fever, a persistently abnormal pattern of bowel movements, abdominal pain, unusual skin lesions or other new symptoms should prompt a return visit to the physician. Appropriate studies should then proceed, with the possibility of common and exotic pathogens in mind. In fact, as conditions acquired during travel may present sometime later, a travel history is always recommended in the evaluation of any patient.

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35. DuPont HL, Sullivan P, Pickering LK, et al: Symptomatic treatment of diarrhea with bismuth subsalicylate among students attending a Mexican University. Gastroenterology 1977 Oct; 73:715-718

36. Merson MH, Sack RB, Islan S, et al: Tetracycline therapy of enterotoxigenic *Escherichia coli* diarrhea, abstract No. 401. 17th Interscience Conference on Antimicrobial Agents and Chemotherapy, New York, Oct 1977

37. Pickering LK, DuPont HL, Olarte J: Single-dose tetracycline therapy for shigellosis in adults. JAMA 1978 Feb; 239:853-854

38. Dupont HL, Reves RR, Galindo E, et al: Treatment of travelers' diarrhea with trimethoprim/sulfamethoxazole and with trimethroprim alone. N Engl J Med 1982 Sep 30; 307:841-844

Book Reviews

The Western Journal of Medicine *does not review all books sent by publishers, although information about new books received is printed elsewhere in the journal as space permits. Prices quoted are those given by the publishers.*

PATHOLOGY OF DRUG-INDUCED AND TOXIC DISEASES—Edited by Robert H. Riddell, MB, BS, MRCPath, Associate Professor, Department of Pathology, University of Chicago. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1982. 682 pages, $79.50.

In the introduction, Riddell points out that this text was prepared to provide pathologists with a comprehensive, well-referenced work concerning specific drug- and toxin-induced diseases of histological reaction. One goal is to provide the information to determine if the observed pathology has any features that distinguishes it from similar lesions occurring in patients not taking the drugs. It is intended that this text be a "reference work."

The introductory chapter, "When is a Disease Drug-Induced," by Irey, indicates clearly the problems involved in relating drug exposure to diseases in humans. The following two sentences set the tone for the book: "Drugs and chemicals can produce in the human body the same spectrum of tissue changes that occur in diseases not caused by drugs and chemicals. Nor, with rare exceptions, are there any clinical or pathological 'markers' that *per se* differentiate adverse drug reactions from other diseases." This chapter written by Irey is quite important and informational. It poses a number of the problems that are not answered in many of the following chapters.

The variability in the presentations is a by-product of a multiauthor text. The section on the effects on the fetus, infant and young child represents an almost encylopaedic presentation, covering multiple systems and pointing to approaches that should be taken to ascertain the nature of the disease. The section on muscle biopsies provides an interesting introduction and several electron micrographs. Unfortunately, the emphasis, which is primarily on diphenylamine poisoning for illustrative reasons, fails to make note of a variety of other induced muscle diseases. The section on hematopoietic responses is, again, a catalogue. Some interesting comments are made concerning bone marrow suppression by chloramphenicol. The discussion of lymphopoietic changes is more extensive, but there is little resort to definitive typing of the type and kind of response, the variety of lymphocytes involved and the significance of changes in these lymphocyte subsets. Immunohistochemical techniques and electron microscopy, as a further definitive approach to understanding drug-induced disease, are not frequently discussed. The section on lung disease is extensive and accompanied by a reasonable set of references.

Probably the biggest problem with this text is that it represents in large part a compilation of anecdotal incidences of drug-related disease. Assumptions are made that specific diseases are caused by chemicals, providing authoritative statements in text form that are not necessarily true and not consistent with the warning cited by Irey in the first chapter. This occurs repeatedly throughout the text without specific reference to understanding the physiological and pathological changes that occur within the cells and may or may not be the result of the chemical agent in question. There is a cataloging of opinion, but not necessarily of fact. For example, the brief comment concerning Vacor and the uniqueness of its effect on the islet cell of the pancreas is dismissed without discussion of the fact that this unusual and rather specific change occurs in humans in contrast to rodents, or even other primates. The description of the modification of the proximal tubule following halogenated hydrocarbon poisoning in man does not make use of the wealth of information that is readily available in extrapolation of pathological data from animals, in fact it does not even consider sublethal cell injury. There are cited references to the potential of enflurane producing a specific hepatocellular necrosis, but in point of fact these data have not been defined and may represent a remarkable overstatement.

The text, therefore, does not represent a well-referenced work. I would even disagree with the comment made by the author that "pathologists as a group tend not to share the same awareness of the possible effects of drugs as clinicians, particularly with increasing number of therapeutic agents available." Perhaps what pathology needs is a more critical review of science, and this text illustrates that perhaps pathologists should be more attentive to the nuances of modern abnormal biology. It is unfortunate that some of the better presentations in the text are hidden in a variety of less-scientifically attuned descriptions of ill-defined disease relationships. The whole is marred by the juxtaposition of detailed analyses by uncritical and superficial reporting.

EDWARD A. SMUCKLER, MD, PhD
Professor and Chairman
Department of Pathology
University of California, San Francisco

* * *

OPERATIVE HAND SURGERY—Volumes 1 and 2— Edited by David P. Green, MD, Clinical Professor of Orthopaedics; Former Chief, Hand Surgery Service, University of Texas Health Science Center at San Antonio. Churchill Livingstone Inc., 1560 Broadway, New York, NY 10036, 1982. 1,754 pages, in 2 volumes, $170.00.

The first comprehensive volume about surgical treatment of hands was written by Sterling Bunnell, a San Francisco surgeon. Bunnell's text, *Surgery of the Hand,* was published in 1944 and was immediately recognized as a classic; it retains its eminence even with all the material that has been written on the subject during the past 38 years. The breadth of surgical treatment of hands has expanded in both manual techniques and basic science knowledge until no one surgeon today can be expert in all phases of this subspecialty. Dr. Green has edited a multiauthored text which presents such a wealth of current information on such a wide range of pertinent subjects that it might be considered the most comprehensive book on operative hand surgical procedures since Sterling Bunnell's masterpiece.

The text comprises 53 chapters under headings such as amputation, arthrodesis, arthroplasty, cerebral palsy and stroke, congenital deformities, fractures and dislocations, infections, microvascular surgery, nails, nerve reconstruction, rheumatoid arthritis, open injuries and tendon reconstruction. The 64 authors have established credentials and expertise in the surgical area about which each has written. Each author presents a complete and impartial perspective of his subject and references average 107 entries per chapter. The quality of the book is enhanced by the medical illustrations. The paper and binding are of good quality.

This book should be in the personal library of all surgeons who operate on the upper extremity. Library copies should be available for nurses, therapists and technicians involved in the care and rehabilitation of hands. This is a comprehensive textbook of major importance in its field of interest.

GEORGE E. OMER, JR, MD
Professor and Chairman
Department of Orthopaedics and Rehabilitation
University of New Mexico
Albuquerque

In Memoriam

California Medical Association

BERNSTEIN, HENRY C., San Francisco. Died January 9, 1983, in San Francisco, aged 67. Graduate of the University of California Medical School, Berkeley-San Francisco, 1940. Licensed in California in 1940. Dr Bernstein was a member of the San Francisco Medical Society.

DAVIDSON, JAMES D., Berkeley. Died December 27, 1982, in Oakland, aged 66. Graduate of the University of Michigan Medical School, Ann Arbor, 1943. Licensed in California in 1948. Dr Davidson was a retired member of the Alameda-Contra Costa Medical Association.

FISHER, H. RUSSELL, Glendale. Died in January 1983, aged 77. Graduate of Hahnemann Medical College and Hospital, Philadelphia, 1928. Licensed in California in 1946. Dr Fisher was a member of the Los Angeles County Medical Association.

HATCHER, CLY HOWARD, Palto Alto. Died December 29, 1982, in Stanford University Hospital of myocardial infarction, aged 82. Graduate of the University of California Medical School, Berkeley-San Francisco, 1929. Licensed in California in 1929. Dr Hatcher was a retired member of the Santa Clara County Medical Society.

HATFIELD, HOWARD L., Pasadena. Died January 6, 1983, aged 85. Graduate of Rush Medical College, Chicago, 1924. Licensed in California in 1924. Dr Hatfield was a member of the Los Angeles County Medical Association.

HULL, EUGENE H., San Bernardino. Died January 8, 1983, in Oceanside, aged 85. Graduate of Emory University School of Medicine, Atlanta, 1920. Licensed in California in 1923. Dr Hull was a retired member of the San Bernardino County Medical Society.

JOSEPH, MARSHALL STUART, San Francisco. Died November 27, 1982, in San Francisco, aged 30. Graduate of Georgetown University School of Medicine, Washington, DC, 1978. Licensed in California in 1979. Dr Joseph was a member of the California House Officer Society.

O'HALLORAN, JAMES P., San Jose. Died in November 1982, aged 56. Graduate of the Creighton University School of Medicine, Omaha, 1952. Licensed in California in 1961. Dr O'Halloran was a member of the Santa Clara County Medical Society.

RAFATY, F. MARK, Palo Alto. Died January 5, 1983, at Stanford University Hospital, aged 49. Graduate of the University of California Medical School, San Francisco, 1964. Licensed in California in 1965. Dr Rafaty was a member of the Santa Clara County Medical Society.

SMITH, ROBIN, Canoga Park. Died January 31, 1983, aged 64. Graduate of the University of Wisconsin School of Medicine, Madison, 1945. Licensed in California in 1954. Dr Smith was a member of the Los Angeles County Medical Association.

Washington State Medical Association

BARNER, HENRY A., Bremerton. Died January 24, 1983, in Bremerton, aged 88. Graduate of the University of Minnesota Medical School, Minneapolis, 1919. Licensed in Washington in 1922. Dr Barner was a retired member of the Kitsap County Medical Society.

GALBRAITH, JAMES E., Seattle. Died January 10, 1983, in Seattle, aged 70. Graduate of the University of Oregon Medical School, Portland, 1940. Licensed in Washington in 1942. Dr Galbraith was a retired member of the Whitman County Medical Society.

HIGHSMITH, LARUE S., Worley, Idaho. Died September 16, 1982, aged 69. Graduate of Northwestern University Medical School, Chicago, 1937. Licensed in Washington in 1948. Dr Highsmith was a retired member of the Spokane County Medical Society.

KRETZLER, HARRY H., SR., Edmonds. Died December 31, 1982, in Seattle, aged 86. Graduate of the University of Nebraska College of Medicine, Omaha, 1923. Licensed in Washington in 1924. Dr Kretzler was a member of the King County Medical Society.

LINDAHL, WALLACE W., Seattle. Died September 7, 1982, in Seattle, aged 70. Graduate of Northwestern University Medical School, Chicago, 1938. Licensed in Washington in 1946. Dr Lindahl was a retired member of the King County Medical Society.

PFLUEGER, JESSE P., Grayland. Died December 21, 1982, aged 69. Graduate of the University of Washington School of Medicine, Seattle, 1950. Licensed in Washington in 1951. Dr Pflueger was a retired member of the Grant County Medical Society.

RIPLEY, HERBERT, Seattle. Died October 8, 1982, aged 75. Graduate of Harvard Medical School, Boston, 1933. Licensed in Washington in 1949. Dr Ripley was a member of the King County Medical Society.

SANDERSON, ERIC R., Seattle. Died December 30, 1982, aged 68. Graduate of Harvard Medical School, Boston, 1937. Licensed in Washington in 1946. Dr Sanderson was a member of the King County Medical Society.

SWANSON, FLORENCE L., Spokane. Died December 16, 1982, aged 79. Graduate of the University of Oregon Medical School, Portland, 1933. Licensed in Washington in 1947. Dr Swanson was a retired member of the Spokane County Medical Society.

TOMPKINS, MORTON W., Walla Walla. Died January 23, 1983, in Tucson, Arizona, aged 71. Graduate of the University of Oregon Medical School, Portland, 1937. Licensed in Washington in 1939. Dr Tompkins was a retired member of the Walla Walla Valley Medical Society.

WMS

ANNUAL MEETING & SCIENTIFIC PROGRAM SCHEDULE

JUNE 29 - JULY 2 1983

PROGRAM

WEDNESDAY, JUNE 29

8:30 am
WMS HOUSE OF DELEGATES OPENING SESSION

1:30 pm
WILLIAM J. KANE, MD
What Is Good Geriatric Care?

2:30 pm
GILBERT S. GORDAN, MD, PhD
Update on Osteoporosis, 1983

3:00 pm
WILLIAM J. KANE, MD
Assessment of the Geriatric Patient in the Ambulatory Setting

4:00 pm
GILBERT S. GORDAN, MD, PhD
Are There Risks to Estrogen Therapy?

THURSDAY, JUNE 30

9:00 am
WILLIAM D. BONDAREFF, MD, PhD
Practical Psychiatry for the Elderly

10:00 am
ROBERT L. DICKMAN, MD
Hypertension in the Elderly

11:00 am
BRUCE PERRY, MD
Falls in the Elderly

1:30 pm to 5:00 pm
KERMIT E. KRANTZ, MD
ERIC W. SPRINGER, JD
Malpractice Risk Management Seminar

FRIDAY, JULY 1

8:45 am
ANANTH K. SHENOY, PhD
Pharmacology—Consequence of Altered Physiology in the Elderly

9:30 am
ROBERT L. DICKMAN, MD
Rational Drug Therapy in the Elderly

10:15 am
WILLIAM J. KANE, MD
Infections in an Aging Population

11:00 am
GERALD L. MESSERSCHMIDT, MD
Care of the Terminal Patient

SATURDAY, JULY 2

9:00 am to 10:30 am
WMS HOUSE OF DELEGATES CLOSING SESSION

FACULTY

WILLIAM D. BONDAREFF, MD, PhD
Professor, Gerontology and Psychiatry
Director, Division of Geriatric Psychiatry
University of California School of Medicine
Los Angeles, California

ROBERT L. DICKMAN, MD
Director, Department of Family Medicine
Assistant Professor of Family Medicine
The Mt Sinai Medical Center
Cleveland, Ohio

GILBERT S. GORDAN, MD, PhD
Professor of Medicine
University of California School of Medicine
San Francisco, California

WILLIAM J. KANE, MD
Vice President for Medical Affairs
Burlington County Memorial Hospital
Mt. Holly, New Jersey

KERMIT E. KRANTZ, MD
Professor and Chairman, Department of Obstetrics and Gynecology
University of Kansas
Bell Memorial Hospital
Kansas City, Kansas

GERALD L. MESSERSCHMIDT, MD
Head of Bone Marrow Transplant
Wilford Hall, USAF Medical Center
Lackland Air Force Base, Texas

BRUCE PERRY, MD
Family Physician
Group Health Medical Center
Lynnwood, Washington

ANANTH K. SHENOY, PhD
Regional Medical Associate
Smith Kline and French Laboratories
Adjunct Assistant Professor
Biochemical Pharmacology and Toxicology
University of Utah
Salt Lake City, Utah

ERIC W. SPRINGER, JD
Horty, Springer and Mattern
Adjunct Professor of Hospital Law
University of Pittsburgh
Pittsburgh, Pennsylvania

THE MEETING WILL BE HELD AT THE JACKSON LAKE LODGE, MORAN, WYOMING

WYOMING Medical Society

For Program, Reservations and Information Contact:

WYOMING MEDICAL SOCIETY
P.O. DRAWER 4009
CHEYENNE, WY 82003
Telephone (307) 635-2424

Magnesium Therapy for Intractable Ventricular Tachyarrhythmias in Normomagnesemic Patients

LLOYD T. ISERI, MD; PETER CHUNG, MD, *and* JONATHAN TOBIS, MD, *Orange, California*

Intractable ventricular tachyarrhythmia associated with hypomagnesemia responds well to magnesium given intravenously. Two patients with recurrent ventricular tachycardia and ventricular fibrillation associated with normal serum magnesium levels and resistant to treatment with potassium chloride, lidocaine and bretylium tosylate responded dramatically to the administration of magnesium sulfate. A third patient in whom the serum magnesium level was unknown also showed dramatic response to magnesium therapy.

Magnesium depletion probably interferes with sodium-potassium adenosine triphosphatase enzyme activity and causes ionic imbalance and electrical instability of Purkinje's fibers. Without obvious magnesium depletion this element in high concentration may still prolong transient inward current, prolong the effective refractory period, increase the membrane potential and control ventricular tachyarrhythmia.

When ventricular fibrillation or malignant ventricular tachycardia cannot be controlled with lidocaine and other conventional drugs, we recommend infusing magnesium sulfate, 2 to 3 grams in one minute, followed by 10 grams over five hours.

Repeated episodes of ventricular tachycardia and ventricular fibrillation requiring cardioversion and administration of lidocaine, procainamide hydrochloride, bretylium tosylate and potassium chloride are frequently encountered in patients with ischemic heart disease. The value of magnesium in correcting these potentially lethal dysrhythmias in hypomagnesemic patients has been well established,[1,2] but its role in treating patients with normal serum magnesium levels has not been described or documented. We report two cases of ischemic heart disease in which the patients had normal serum magnesium levels and in which magnesium sulfate was used successfully to treat intractable ventricular tachycardia and ventricular fibrillation. A third case in which the patient's serum magnesium level was unknown and there were repeated episodes of ventricular fibrillation is also presented.

Reports of Cases

CASE 1. The patient, a 75-year-old woman with a permanent epicardial pacemaker, was admitted to hospital because of dizziness and faintness. A year before she had had an episode of ventricular tachycardia and procainamide therapy was begun but because of a lupus reaction the drug was discontinued. She had been receiving quinidine, furosemide, potassium chloride, propranolol hydrochloride and levothyroxine. Propranolol therapy was stopped two days before admission because of the development of congestive heart failure. Digoxin was not prescribed. The blood pressure was 100/60 mm of mercury and the heart was being paced at 82 per minute. The lungs were clear, heart sounds were normal and there was no edema. The serum sodium level was 143, potassium 2.9 and magnesium 1.6 mEq per liter; quinidine concentration was 2.4 μg per ml and creatine kinase 26 units per liter (Figure 1). Arterial blood gas determinations done with the patient breathing room air showed a pH of 7.44, a partial carbon dioxide pressure (P_{CO_2}) of 36 mm of mercury and a partial oxygen pressure (P_{O_2}) of 90 mm of mercury. In the emergency room, she had several episodes of ventricular tachycardia converted with precordial thump or by countershock. She was given lidocaine and admitted to the intensive care unit where she continued to have recurrent ventricular tachycardia and ventricular fibrillation. She was given by mouth potassium chloride, 20 mEq every six hours, and quinidine, 300 mg every six hours, and the following drugs intravenously: potassium chloride, 5 mEq per hour; lidocaine, 50, 75 and 75 mg, followed by 4 mg per minute by infusion;

Refer to: Iseri LT, Chung P, Tobis J: Magnesium therapy for intractable ventricular tachyarrhythmias in normomagnesemic patients. West J Med 1983 Jun; 138:823-828.

From the Division of Cardiology, Department of Medicine, California College of Medicine, and University of California Irvine Medical Center, Orange.

Submitted, revised, November 3, 1982.

Reprint requests to Lloyd T. Iseri, MD, Professor of Medicine, Division of Cardiology, UCI Medical Center, 101 City Drive So, Orange, CA 92668.

ABBREVIATIONS USED IN TEXT

P_{CO_2} = partial carbon dioxide pressure
P_{O_2} = partial oxygen pressure

propranolol, 5 mg four times in one hour, and bretylium, 300, 600 and 900 mg, followed by 2 mg per minute by infusion. Lidocaine administration was stopped because of toxic symptoms and a serum concentration of 7 μg per ml. Despite these medications and return of the serum potassium value to 4.1 mEq per liter and the spontaneous rise of the magnesium value to 2.6 mEq per liter, the patient continued to have recurrent ventricular tachycardia and ventricular fibrillation requiring a total of 30 direct-current countershocks in a 24-hour period (Figure 2). Magnesium sulfate was then given intravenously at a dose of 16 mEq over 20 minutes followed by an intravenous infusion at 8 mEq per hour. Except for one short run of ventricular tachycardia, which converted spontaneously, there were no further episodes and cardiac rhythm became stable with a continuously paced mode. The serum magnesium level four hours after starting therapy was 3.7 mEq per liter, rising to 4.2 mEq per liter eight hours later. The blood pressure began to fall but rose to control levels after bretylium administration was stopped.

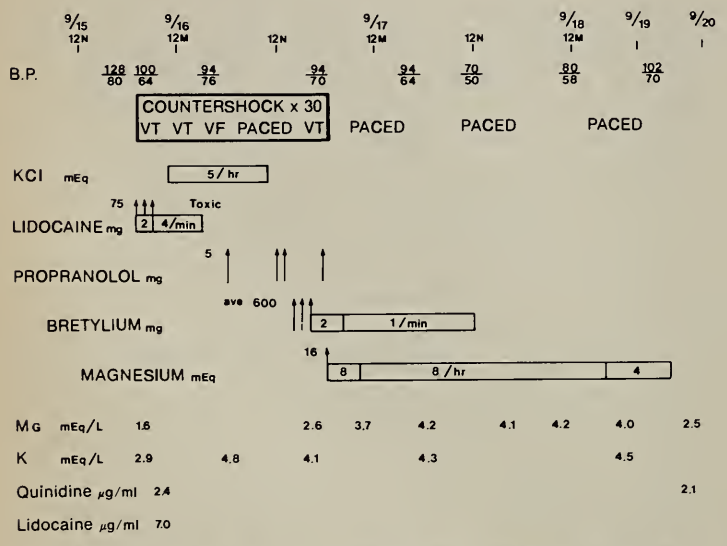

Figure 1.—Diagram showing response to treatment of patient in case 1. The patient had recurrent ventricular tachycardia (VT) and ventricular fibrillation (VF). B.P. = blood pressure, KCl = potassium chloride, Mg = magnesium, K = potassium.

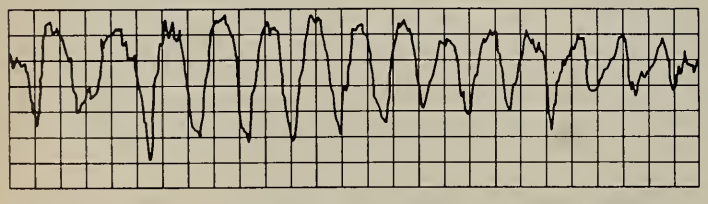

Figure 2.—Electrocardiographic rhythm strip from patient in case 1 showing coarse ventricular fibrillation.

Cardiac catheterization two weeks later showed complete occlusion of the left anterior descending, 75 percent occlusion of the right coronary and 75 percent occlusion of the circumflex arteries and an apical aneurysm. Cardiac output was 2.1 liters per minute and the pulmonary artery wedge pressure was 7 mm of mercury. Two weeks later a three-vessel saphenous vein bypass surgical procedure was done and the patient was discharged in stable condition 2½ weeks later.

Comment. The development of recurrent ventricular tachycardia and fibrillation in this patient was most probably the result of multiple factors involving myocardial ischemia, a tendency to hypopotassemia, quinidine therapy and propranolol withdrawal. The electrocardiographic findings originally resembled "torsades de pointes." A valiant effort was made to control the life-threatening arrhythmia. Lidocaine, bretylium, potassium chloride and propranolol were given to maximal doses without success. Finally, even with normal serum levels, magnesium sulfate was given intravenously with a dramatic cessation of ventricular tachycardia and fibrillation.

CASE 2. The patient, a 58-year-old woman, was admitted with severe congestive heart failure. She had had two coronary artery bypass procedures and a porcine mitral valve replacement six months before. She had been taking digoxin, furosemide, potassium chloride, quinidine and hydralazine hydrochloride. She had distended neck veins, atrial fibrillation, pulmonary rales, a pansystolic apical murmur and mild ankle edema. Her blood pressure was 100/62 mm of mercury, pulse rate 88 per minute, respirations 22 and temperature 36.5°C (97.7°F). Her weight was 62 kg. Laboratory studies gave the following values (Figure 3): serum potassium, 3.8, sodium, 140, and magnesium, 1.9 mEq per liter; creatinine, 1.5 mg per dl; creatine kinase, 12 units per

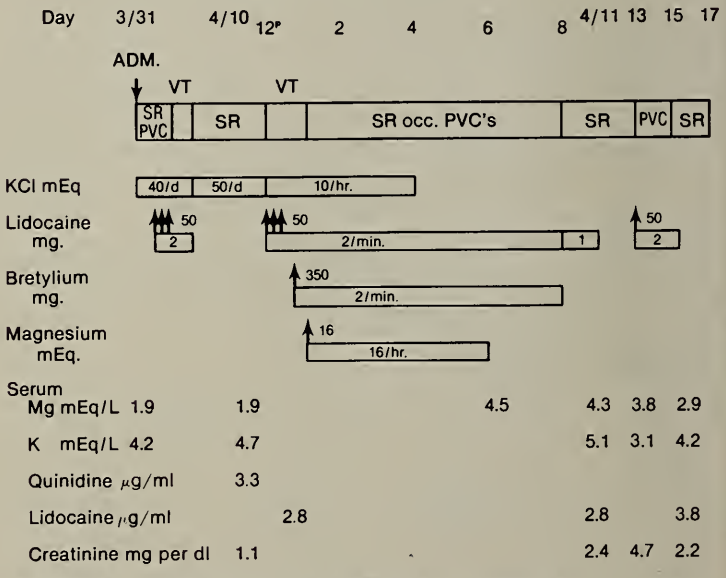

Figure 3.—Diagram showing response to treatment of patient in case 2. The patient had recurrent ventricular tachycardia (VT), with dramatic return to sinus rhythm (SR) and occasional premature ventricular contractions (PVC) following administration of magnesium sulfate. KCl = potassium chloride, Mg = magnesium, K = potassium.

liter; quinidine concentration, 2.9 μg per ml; digoxin content, 1.6 ng per ml; arterial blood pH, 7.49, P_{CO_2}, 24.6 mm of mercury, and P_{O_2}, 90.1 mm of mercury.

Pulmonary congestion was relieved by giving high doses of furosemide supplemented with potassium chloride. On the second day, short runs of ventricular tachycardia developed, controlled by giving lidocaine intravenously, followed by quinidine by mouth, with serum concentrations of 2.4 to 4.3 μg per ml.

Cardiac catheterization done on the eighth day showed an akinetic posterobasal ventricular aneurysm, 2+ mitral regurgitation, occluded native right coronary and circumflex arteries and severely diseased left main and proximal anterior descending arteries. The graft to the mid-anterior descending artery was patent but the grafts to the right coronary and circumflex arteries were not seen. The pulmonary artery pressure was 55/25 mm of mercury and the wedge pressure was 14.7 mm of mercury. The cardiac index was 1.73 liters per minute per sq m and there was evidence of pericardial thickening. The ejection fraction was 59 percent.

On the 11th day, the patient had cough, chills and fever, became hypoxic and had a cardiac arrest with a quick series of 5- to 20-second ventricular beats electrocardiographically resembling torsades de pointes (Figure 4).[3] Arterial blood gas determinations made with the patient breathing oxygen by mask showed a pH of 7.54, P_{CO_2} 21.2 and P_{O_2} 61.5 mm of mercury. Laboratory studies disclosed the following values: serum potassium, 4.7, and magnesium, 1.9 mEq per liter; quinidine, 3.3 μg per ml; digoxin, 1.4 ng per ml, and creatinine, 1.1 mg per dl. The patient responded only partially to lidocaine with a serum concentration of 2.8 μg per ml, and frequent multifocal premature ventricular beats of up to six in sequence continued to recur despite the administration of lidocaine and full doses (350 mg) of bretylium. After an endotracheal tube was inserted the arterial blood gas studies showed a pH of 7.45, P_{CO_2} 26.7 and P_{O_2} 88.6 mm of mercury. Ventricular tachycardia however contained to recur. The blood pressure also fell from 110/60 to 90/58 mm of mercury. Administration of magnesium sulfate, 10 ml of 20 percent solution given intravenously over one minute, followed by infusion of 2 percent solution at 100 ml per hour for five hours, promptly eliminated the episodes of ventricular tachycardia and sharply reduced the total number of ectopic premature ventricular beats from 45 a minute to 3 a minute (Figure 5). Administration of both lidocaine and bretylium was continued at 2 mg per minute. Because of a further fall in the blood pressure to 78/40 mm of mercury, bretylium therapy was discontinued. This was promptly followed by a rise in the blood pressure to 96/52 mm of mercury. Pneumonia developed, which was treated with gentamicin sulfate and nafcillin sodium. On the following morning the serum potassium value was 5.1, magnesium 4.5 and sodium 127 mEq per liter, and the creatinine level 3.4 mg per dl. The endotracheal tube was removed and the patient's condition stabilized on a regimen of procainamide, digoxin, furosemide, captopril, spironolactone and potassium chloride. After gradual improvement of her cardiopulmonary and renal functions, she was discharged from hospital on the 43rd day.

Comment. In this patient who has advanced coronary

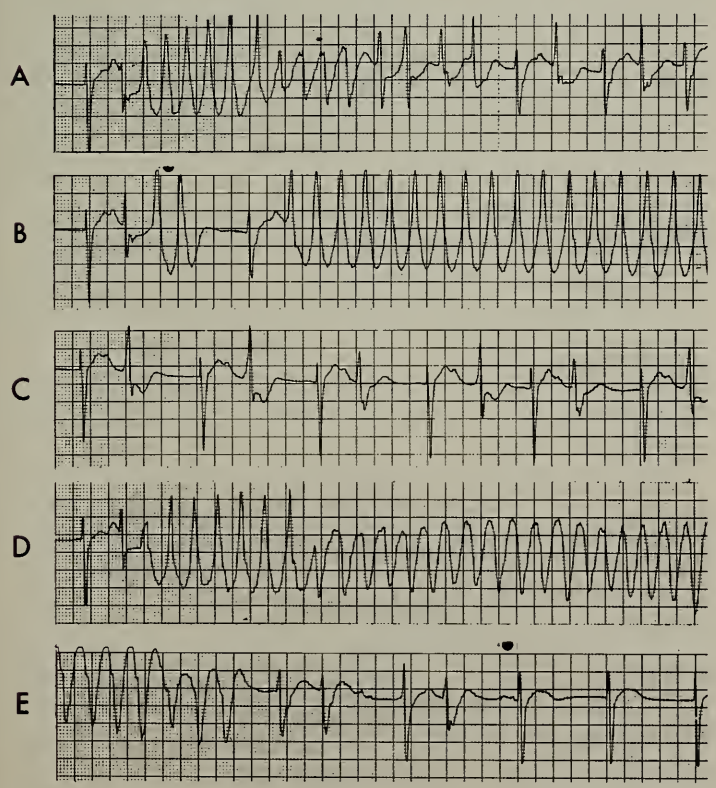

Figure 4.—Electrocardiographic tracings from patient in case 2 showing episodes of ventricular tachycardia resembling torsades de pointes.

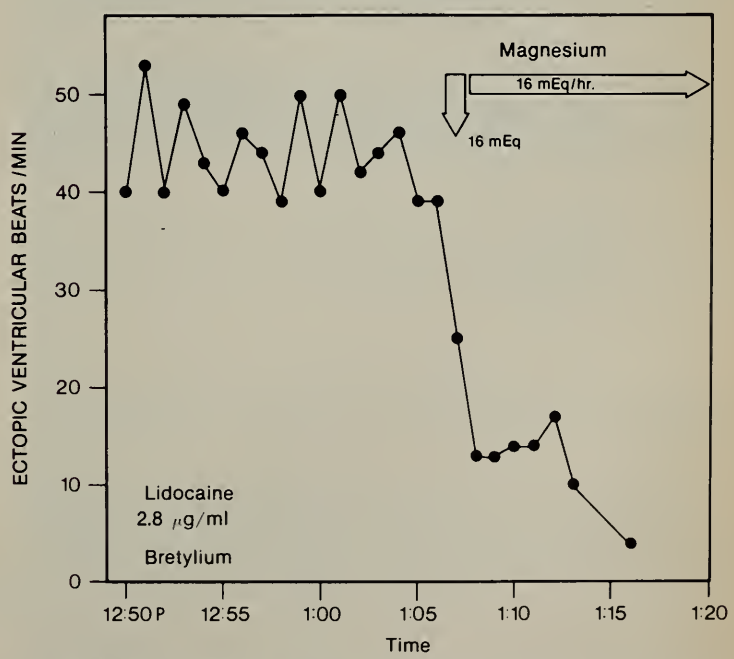

Figure 5.—Schematic showing ventricular response in patient in case 2 following magnesium therapy. The average of 45 ectopic ventricular beats per minute before magnesium therapy represents 30 episodes of ventricular tachycardia in a 15-minute period. After magnesium therapy, no episodes of ventricular tachycardia were seen, except for two runs of three ectopic beats.

artery and valvular heart disease and ventricular aneurysm, recurrent ventricular tachycardia most probably developed because of hypoxia and respiratory alkalosis from pneumonia. Quinidine concentration in the blood had fallen from 4.3 to 3.3 μg per ml at the time of recurrence of ventricular tachycardia. The digoxin concentration was within the therapeutic range. Serum potassium and magnesium levels were also within normal limits.

Recurrence of ventricular tachycardia could not be controlled by lidocaine or bretylium infusion or by endotracheal intubation and improvement of blood gas values. Additional boluses of bretylium were not given because of a drop in the blood pressure. Control of the rhythm, on the other hand, was quite dramatic following the infusion of magnesium sulfate (Figure 5). Episodes of ventricular tachycardia ceased immediately and the number of ectopic ventricular beats per minute fell sharply.

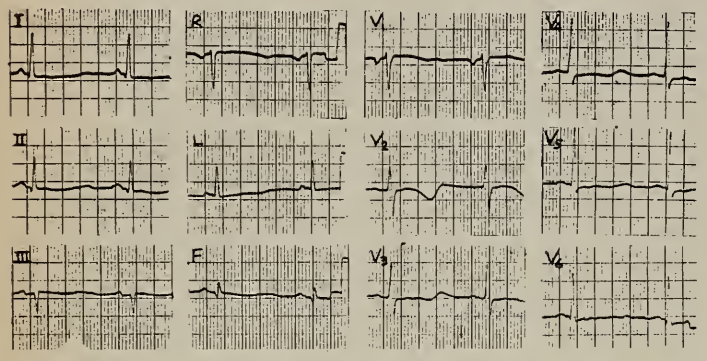

Figure 6.—A 12-lead electrocardiogram done on the patient in case 3 on admission to hospital.

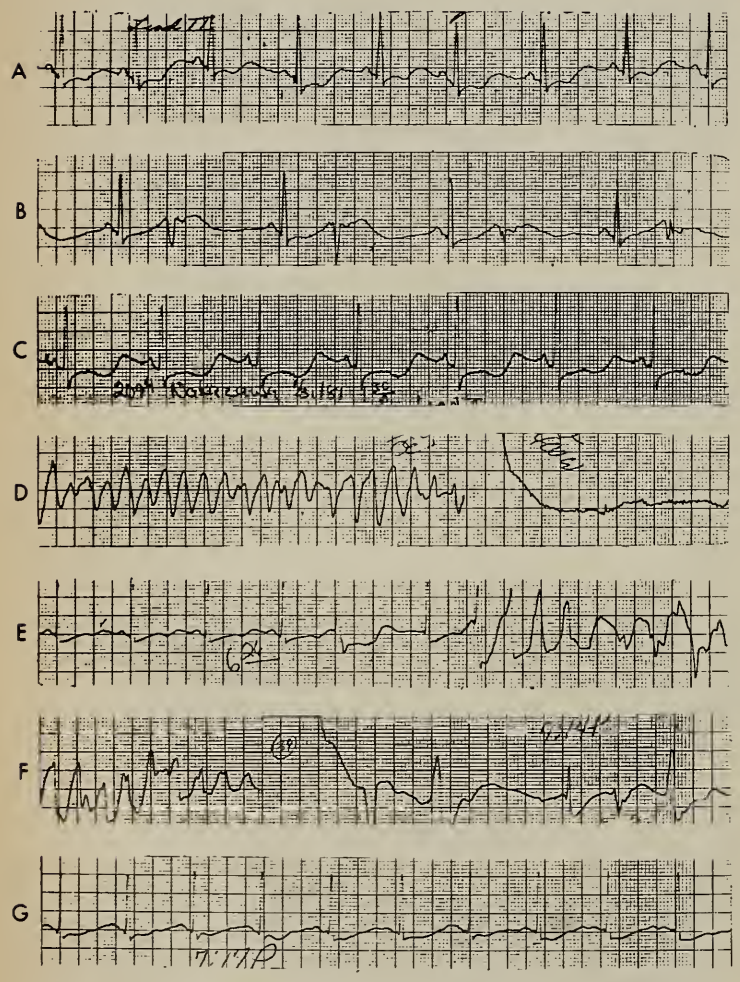

Figure 7.—Representative electrocardiographic tracings of patient in case 3 of hypopotassemia, premature ventricular contractions and repeated episodes of ventricular fibrillation.

Case 3. The patient, a 58-year-old male pharmacist, was brought to a local hospital after fainting while driving on the freeway and damaging his car; he was not injured. He had had hypertension for four years and a three-vessel coronary artery bypass operation a year before. He had been taking quinidine gluconate, 325 mg twice a day, hydrochlorothiazide, 50 mg a day, metoprolol tartrate, 25 mg twice a day, and potassium chloride, 16 mEq a day. He said he had had no recent chest pains, shortness of breath, dizziness or syncope.

On admission the blood pressure was 170/100 mm of mercury. The pulse rate was regular at 60 per minute. He weighed about 70 kg. Lung fields were clear and heart sounds were normal. There was no edema. The electrocardiogram showed a sinus bradycardia at 55 per minute, apparent QT prolongation with prominent U waves and probably an old inferior wall infarction (Figures 6 and 7-A). Laboratory studies disclosed the following values: serum potassium, 2.4 mEq per liter; sodium, 140 mEq per liter; blood urea nitrogen, 9 mg per dl; creatinine, 1.2 mg per dl; chloride, 100 mEq per liter, and serum quinidine, 1.8 μg per ml. Serum creatine kinase level was 40 units per liter, α-hydroxybutyrate dehydrogenase, 179 units per ml (normal, 140 to 350), lactate dehydrogenase, 136 units per ml, and aspartate aminotransferase (formerly, glutamic oxaloacetic transaminase [SGOT]), 24 units per liter. A serum specimen was obtained for a magnesium level, but the results were never reported (Figure 8). During chest x-ray examination, the patient had a transient syncopal episode and the electrocardiogram showed bigeminal premature ventricular beats (Figure 7-B). Measurement of arterial blood gases with the patient breathing room air showed a pH of 7.45, Po_2 of 53.7 mm of mercury, Pco_2 43.2 mm of mercury, a base excess of 5.5 mEq per liter, bicarbonate radical of 29 mEq per liter and oxygen saturation 90 percent. The rhythm appeared to stabilize with potassium chloride infusion and nasal oxygen (Figure 7-C).

About six hours after admission while being observed in the intensive cardiac care unit the patient suddenly had a cardiac arrest with ventricular fibrillation (Figure 7-D) and immediately received 400 joules of countershock. The blood pressure was 160/100 mm of mercury just before the arrest and 240/150 mm of mercury immediately after successful defibrillation. Arterial blood gas determinations made immediately after the arrest showed a pH of 7.53, Po_2 55.6 mm of mercury, Pco_2 34.4 mm of mercury and oxygen saturation 92.5 percent. The serum potassium value was reported later to be 2.6 mEq per liter. Lidocaine, 100 mg intravenously, and 4 mg per minute by intravenous infusion,

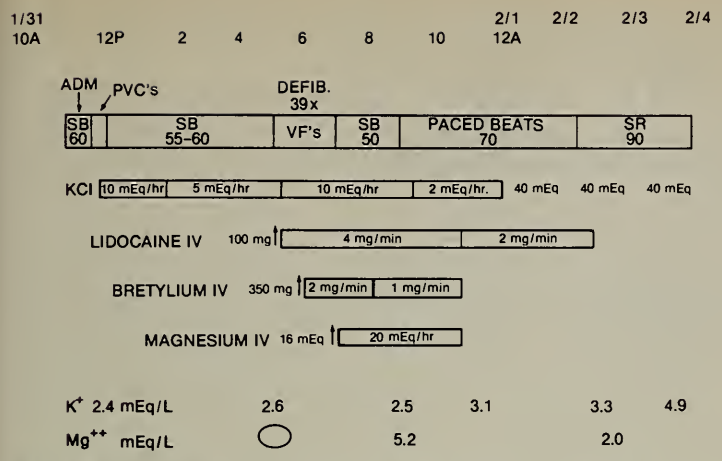

Figure 8.—A schematic showing response to treatment of patient in case 3 who had recurrent ventricular tachycardia and fibrillation. ADM = admission, PVC's = premature ventricular contractions, SB = sinus bradycardia, DEFIB = defibrillation, KCl = potassium chloride, K^+ = potassium, Mg^{++} = magnesium.

was immediately given and the potassium chloride infusion rate was increased to 10 mEq per hour. Despite this management ventricular fibrillation and ventricular tachycardia continued to recur, requiring eight separate countershocks in the next 30 minutes. Numerous periods of torsades de pointes were seen. Bretylium tosylate, 350 mg given intravenously and 2 mg per minute by intravenous infusion, was then added but ventricular fibrillation and tachycardia continued to recur, requiring 31 more countershocks in the next 75 minutes. In desperation, even without knowing the serum magnesium level, magnesium sulfate was infused at a dose of 10 ml of 20 percent solution over one minute, followed by 125 ml of 2 percent solution per hour by intravenous infusion. Immediately following the initial infusion of magnesium sulfate the ventricular tachycardia and fibrillation ceased (Figure 7-G). The blood pressure fell to 180/106 mm of mercury after the administration of bretylium and to 110/80 mm of mercury after we added magnesium. Sinus bradycardia of 50 beats per minute again recurred and a temporary pacemaker electrode was inserted to prevent recurrence of ventricular fibrillation. Serial creatine kinase levels were 2,449, 1,624 and 1,673 units per liter with MB fractions of 3 percent, 4 percent and 4 percent, respectively. These high values were considered to be due to the numerous countershocks.

About 3½ hours after starting magnesium therapy, the deep tendon reflexes at the knees disappeared and the serum magnesium level was 5.2 mEq per liter. Administration of both bretylium and magnesium was stopped and the dose of lidocaine infusion was decreased to 2 mg per minute. Pacing was also discontinued. Procainamide administration, 350 mg four times a day by mouth, was started on the second day to maintain normal rhythm.

A sinus rhythm of 90 per minute supervened and the blood pressure became stable at 130/90 mm of mercury. With potassium chloride supplements, the serum potassium level rose to 3.3 and then to 4.9 mEq per liter. The magnesium level three days later was 2.0 mEq per liter. The pacer electrode was removed and after observation in another hospital for ten days, the patient was discharged. He returned to work as a pharmacist six weeks later.

Comment. The mechanism for this patient's initial syncope resulting in an automobile accident is speculative but the episode he had shortly after being admitted, which was accompanied immediately afterwards by bigeminal premature ventricular beats, suggested that he had transient ventricular tachycardia. Subsequent cardiac arrests preceded by periods of ventricular tachycardia resembling torsades de pointes appeared to confirm this impression (Figure 7-D and E).[3] He had increased the dosage of hydrochlorothiazide without increasing potassium supplements and clearly had hypopotassemia and alkalosis on admission. In addition, the magnesium was probably depleted.[4] The failure of the serum potassium level to rise after he received potassium supplements and the rise in the serum potassium level after magnesium administration supports this notion.

Other factors may have contributed to the development of ventricular tachycardia. The patient was known to have ventricular irritability and had been receiving quinidine gluconate therapy prophylactically. Although the serum quinidine concentration was well below the toxic level it could have caused QT prolongation and the development of torsades de pointes.[5] Hypoxia presumably due to hypopotassemic hypoventilation persisted and may have also aggravated the situation. Although acute myocardial infarction was ruled out, myocardial ischemia is always a threat in patients following a coronary bypass procedure.

Whatever the cause of the ventricular tachycardia and ventricular fibrillation, the dramatic turn of events following magnesium therapy after administration of 60 mEq of potassium chloride, two hours of lidocaine

TABLE 1.—*Laboratory Values in Patients Before Administration of Magnesium Sulfate*

Case	Drug Concentrations: Digoxin ng/ml	Drug Concentrations: Quinidine µg/ml	Diuretic Agent	Serum Values: Potassium mEq/liter	Serum Values: Magnesium mEq/liter	Arterial Blood Gases: pH	Arterial Blood Gases: P_{CO_2} mm/mercury	Arterial Blood Gases: P_{O_2} mm/mercury
1	0.0	2.4	Furosemide	4.1	2.6	7.44	36.0	90.0
2	1.4	3.3	Furosemide	4.7	1.9	7.54	21.2	61.5
3	0.0	1.8	Hydrochlorothiazide	2.6	?	7.45	43.2	53.7

P_{CO_2} = partial carbon dioxide pressure, P_{O_2} = partial oxygen pressure.

therapy and one hour of bretylium therapy had failed attests to the value of magnesium.

Discussion

Magnesium is essential for many enzyme systems, among which is the activation of membrane-bound adenosine triphosphatase controlling transfer of sodium and potassium across the cell membrane.[6] Depression of this enzyme activity results in decreased intracellular potassium and increased intracellular sodium leading to electrical instability of Purkinje's fibers. Undoubtedly when hypomagnesemia is present, intractable tachyarrhythmias can be corrected immediately by magnesium replacement.[2] There is, however, equivocal evidence that when the serum magnesium level is not low, arrhythmias could still be corrected by magnesium.[7] It has been shown recently by direct measurement of skeletal muscles that prolonged diuretic therapy results in a loss of cellular potassium and magnesium.[8] These cellular losses could be prevented by magnesium but not by potassium replacement. The cellular changes did not correlate with plasma concentrations either for potassium or for magnesium.[9] Because all three patients described here were on prolonged diuretic therapy, cellular depletion of these two interlocked elements probably occurred. Whether or not magnesium therapy will protect against ventricular tachyarrhythmia in patients with a normal serum level and without substantial cellular depletion of magnesium cannot be answered. Some evidence suggests, however, that high magnesium levels may prolong the effective refractory period and increase the membrane potential (make more negative). These changes have been suggested as a mechanism of the antiarrhythmic effects of magnesium.[10] Magnesium has also been shown to block the transient inward current generated by cardiotonic steroids.[11] Specificity of magnesium therapy in the treatment of recurrent ventricular fibrillation with a serum digoxin concentration of 20 ng per ml in a recent case was reaffirmed when giving maximum doses of lidocaine and phenytoin (Dilantin) had initially failed. It is entirely possible that a transient inward current not due to digitalis preparations may be responsible for the recurrent ventricular tachycardia and fibrillation described here and that administering magnesium in high doses blocked these currents and was thereby effective in controlling the rhythm.

All three patients were also taking quinidine (Table 1) and the possibility that this drug is responsible for ventricular tachycardia must be strongly considered. However, the successful disruption of recurrent ventricular tachycardia with magnesium despite continued use of quinidine in one case indicated that at least in this case quinidine was not solely responsible for the arrhythmia.[12] If quinidine toxicity indeed was responsible for the arrhythmia in these cases, magnesium would have to be considered an effective antidote. The ionic basis for such a relationship has not been reported.

The importance of these observations lies in the fact that parenteral magnesium therapy may be life-saving in cases of intractable recurring ventricular tachycardia and fibrillation even with normal serum magnesium levels.

We recommend that if lidocaine infusions fail to control these potentially lethal rhythms, magnesium infusion be started immediately along with potassium even before serum levels for these elements are known. Oliguric forms of renal failure resulting in hyperpotassemia and hypermagnesemia will obviously contraindicate such replacement therapy but absence of hyperkalemic electrocardiographic changes and the presence of deep tendon reflexes should give some assurance that neither hyperpotassemia nor hypermagnesemia is present. A "sick sinus syndrome" or evidence of atrioventricular block previously diagnosed or brought to light after cardioversion may necessitate temporary pacing before either magnesium or potassium therapy can be started. Mild hypotension brought on by magnesium therapy is considered no more dangerous than that caused by the administration of procainamide or bretylium and for that reason magnesium infusion can be recommended as a second-line drug in the treatment of recurring ventricular fibrillation.

For intravenous infusion, 10 to 15 ml of 20 percent magnesium sulfate (16 to 24 mEq) solution given slowly for one minute followed by 500 ml of 2 percent magnesium sulfate (80 mEq) solution given over five hours is recommended.[2] Administration of a second bottle of 500 ml of 2 percent magnesium sulfate solution given over ten hours may be necessary in those patients severely depleted of magnesium. Potassium chloride infusion at 10 mEq per hour for five hours is also recommended because there is substantial evidence that potassium and magnesium depletion usually occurs together.[4,13] Needless to say, overdosage with these drugs should be monitored closely with serum levels, electrocardiograms, blood pressure readings and neurologic examinations for such manifestations as loss of deep tendon reflexes.

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Allergic Skin Test Reactivity to Marijuana in the Southwest

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In a general allergy consultation practice in Arizona and western New Mexico, 129 patients were tested for immediate hypersensitivity skin test reactivity to marijuana pollen and tobacco leaf, as well as to a battery of other antigens. In all, 90 patients were diagnosed as allergic (atopic) and, of these, 63 (70 percent) were found to be skin test reactive to marijuana pollen and 18 (20 percent) to tobacco leaf. The incidence of skin test reactivity to marijuana was not significantly different for persons living at low, middle or high elevations throughout the Southwest. Marijuana sensitivity occurred in patients who were, in general, also sensitive to a variety of other airborne plant pollens. There was no close correlation, however, between sensitivity to marijuana pollen and sensitivity to pollens from elm, mulberry, hop and stinging nettle, which are botanically related to marijuana. The data suggest that marijuana pollen may be a relatively common airborne pollen pollutant in the Southwest, allergic persons being sensitized through inhalation. If this is confirmed by further studies, then clinical investigation of marijuana hyposensitization (immunotherapy) may be warranted. This is in contrast to tobacco allergy for which simple avoidance is recommended.

In this study immediate allergy skin test reactions to marijuana *(Cannabis sativa)* pollen and tobacco leaf in a Southwest allergy practice (Arizona and western New Mexico) are reported. Interest in this subject arose because our population now smokes marijuana in addition to tobacco and also grows marijuana plants as illicit crops.

Results suggest that marijuana, a plant prevalent in the Southwest, has a highly allergenic pollen. Allergy to the pollen is common and management of this allergy may eventually require procedures that allergists currently use for other botanical species that produce a sensitizing windborne pollen, such as Bermuda grass, mulberry tree, juniper (mountain cedar) and Russian thistle (tumbleweed).

Methods

Consecutive unselected patients were tested who were seen in a referral practice from August 1980 to February 1981 in nonmetropolitan areas of Arizona and western New Mexico. Testing was done with a battery of allergens that included tobacco leaf (1:20 weight per volume [wt per vol] scratch glycerosaline and 1:1,000 intradermal wt per vol aqueous solution, Greer Laboratories, Lenoir, NC) and the pollens from marijuana *(Cannabis sativa)* (1:20 wt per vol scratch glycerosaline and 500 protein nitrogen units [PNU] per ml intradermal aqueous solution, Hollister Stier Laboratories, Spokane, Wash), mulberry, elm, hop and nettle plants. Several patients were excluded for technical reasons, such as age younger than 6 years.

Test results, read at 20 minutes, were reported on a scale of 0 to 4 according to standard allergy practice,[1(p258)] and borderline reactions were considered negative. Statistical tests for significance were made by x^2 analysis.

Results

In all, 129 patients were studied, ranging in age from 6 to 66 years (82 female and 47 male subjects). Half these patients were adults between ages 19 and 39. Of the 129, there were 90 who were diagnosed as atopic (allergic) on the basis of positive immediate skin test reactions, usually to a variety of allergenic substances such as pollens, molds, house dust and animal danders, as well as an appropriate history or

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Dr Freeman is in private practice in Tucson.
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Submitted, revised, October 25, 1982.
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TABLE 1.—*Skin Test Reactions to Marijuana Pollen and Tobacco Leaf in 129 Patients Studied*

	Patients Tested		
	Male No.=47	Female No.=82	Total No.=129
Allergic patients	35	55	90
Marijuana pollen skin test positive	27	36	63
Tobacco leaf skin test positive	10	8	18

TABLE 2.—*Skin Test Reactions to Marijuana and Other Related Botanical Pollens in 90 Allergic Patients*

	Marijuana Skin Test	
	Positive N=63 Percent	Negative N=27 Percent
Hop skin test positive	49	19
Nettle skin test positive	27	4
Mulberry skin test positive	49	24
Elm skin test positive	53	22

examination (Table 1). These patients had allergic rhinitis, asthma, urticaria or atopic dermatitis or a combination of these. The remaining 39 had completely negative skin tests to all substances tested and were classified as nonallergic patients.

Of the 90 atopic patients, 63 (70 percent) had a positive skin test reaction to marijuana pollen and only 18 (20 percent) reacted to tobacco leaf. No patient reacted only to marijuana pollen or tobacco leaf (or both), supporting the concept that these substances in the concentrations used were neither histamine releasers nor irritants. Marijuana reactors also reacted to other plant pollens, never only to marijuana pollen.

A third of the allergic patients were current or past tobacco smokers; this was unrelated to whether tobacco leaf skin test was positive or negative (not significant at $P=.05$). There were no reliable data for marijuana use in these patients, nor was an attempt made to obtain this information. Patient exposure to marijuana plant pollen was unknown.

Only half the marijuana pollen reactors also reacted to hop, mulberry or elm pollen and only a fourth to nettle pollen (Table 2). Of the 27 allergic patients who did not react to the marijuana, one fourth reacted to elm or mulberry and less to hop or nettle pollen.

Geographic location within Arizona or western New Mexico at the time of testing did not correlate with reactivity to marijuana when patients were grouped according to low, middle and high altitudes (not significant at $P=.01$, data not shown). Most patients, however, had lived at least a year in a different geographic location and it is unknown where they were when the marijuana sensitivity developed. Several of the reactors had lived in only a single location.

Discussion

Arizona Flora[2] in more than 1,000 pages does not list marijuana as a native or imported growing plant in the state or in nearby New Mexico. Tucson newspapers, however, have repeatedly reported seizures of plants by law enforcement agencies, as have news sources in other cities and towns, and suggest that marijuana growth is widespread. In July 1981 the public reporting of marijuana pollen in the daily aerial pollen counts began in Tucson (*Arizona Daily Star,* Tucson, July 17, 1981, p 4A). That marijuana is widely grown in the United States is an accepted fact; the profitable marijuana crop in northern California, for instance, has been estimated at more than $1 billion yearly (*People Weekly Magazine,* 1982 Mar 10; 17:26-28).

The plant order Nettle contains hemp (marijuana) as a family with only one member. Other families in the same order contain hop, nettle, mulberry and elm trees.[3(p510)] Elm and mulberry trees are abundant in many Arizona and New Mexico communities. Wild hop is uncommon but reported in high mountain woods and some nettle grows along water courses.[2] All are windborne-pollen producers, potentially responsible for allergic symptoms in sensitized persons. The fine light pollen of marijuana microscopically resembles nettle. This pollen does not settle well onto open slides used for pollen counts; special procedures (volumetric counters) may be used. Wild tobacco grows throughout the regions in roadside ditches but does not produce a windborne pollen.

Information on skin test reactivity and allergy symptoms from tobacco has been published.[4-6] Anywhere from 8 percent to 64 percent of all persons skin tested to tobacco leaf in past studies had positive reactions, occurring in smokers and nonsmokers, but testing methods used are not comparable between studies. Assessing allergic symptoms from tobacco exposure is difficult because the smoke may be an irritant for many allergic persons and is often disliked. Several cases of true allergic (IgE-mediated) reactions have occurred in tobacco plant production workers.[7]

In contrast, there is little information on skin test results or clinical allergy to marijuana, perhaps because it is an illegal substance but also because allergists do not include it in the general battery of tests. In the Midwest where marijuana grows wild, physicians have gathered unpublished findings of positive skin test reactions to the pollen, and this has been considered a possible cross-reaction to nettle, hop or some other related substance (Robert A. Stier, MD, written communication, July 8, 1980).

All parts of the marijuana plant are smoked or ingested as a recreational drug. Irritating bronchial and central nervous system effects from marijuana use have overshadowed its weak but definite prolonged bronchodilator effect in asthma (by smoke or ingestion) that otherwise might be useful.[8,9] There are several recorded cases of asthma and anaphylaxis from marijuana smoking.[10]

Elevated IgE levels are reported in sera from both tobacco and marijuana users[11] but other general immunologic abnormalities have not been found.[12]

In our patients sensitivity to marijuana pollen was

three times as common by skin test as to tobacco leaf in the allergic persons. This finding suggests that marijuana pollen is highly sensitizing; that marijuana skin test reactivity is not a cross-reaction to closely related mulberry, elm, hop or nettle pollen, and that marijuana pollen is not an irritant or histamine releaser in the skin test procedures used. The reactions to marijuana were not related to patients' sex or the altitude at which they lived, which affects plant distribution.

No reliable histories were obtained for marijuana use in these private patients on this sensitive issue. Any relationship between exposure from use of the marijuana plant as a recreational drug and that from inhaling the airborne pollen is unknown. Some anecdotal information was given by many that suggested widespread growth of the plants in many communities of the area.

Pollen counts for marijuana will need to be looked at in all communities to determine its presence in the air. It is possible that the pollen may produce sensitization in some allergic law enforcement agents exposed at work. One worker was quoted as follows: "It's miserable to work around. . . . Some people come in here and get runny noses or their skin breaks out because they have allergies" (*Arizona Daily Star,* Tucson, August 22, 1980, p 1B). Local monitoring of the pollen in the air in the summer pollinating period might identify the sites within communities where it is being grown and thus be of importance in law enforcement.

The primary importance of marijuana to an allergic patient is probably in its presence as a crop that produces the sensitizing airborne pollen and thus is potentially responsible for some allergic asthma and rhinitis. This is in contrast to tobacco in which the health hazard to allergic persons is from working in tobacco factories, from smoking and possibly from passive exposure to smoke. If an allergic person lives where marijuana is grown and becomes sensitized to its pollen, it may be appropriate eventually to give treatment with immunotherapy (hyposensitization) injections, just as treatment is given now for other local pollens. This treatment consideration will require further studies that evaluate the presence of airborne marijuana pollen in communities, its correlation with patient symptoms and, by reproducing the symptoms, establish that the pollen can produce allergies.

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Varicocele in Youth

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Thirty boys 8 to 18 years of age seen in a general urologic practice with emphasis on pediatrics had palpable varicoceles. A concomitant finding was that 77 percent of these patients had a smaller testis on the left side. Because the small testis is present before maturity, its size appears due to arrest of testicular growth rather than to atrophy.

Surgical correction is advisable when the varicocele is pronounced, the involved testis is distinctly smaller or there is scrotal pain.

Thirty patients 8 to 18 years of age seen between 1955 and 1978 in our private practice had a palpable varicocele at presentation. The left testis was smaller than the right in 77 percent of these patients and, in 10 percent, so much smaller that it was considered abnormal, either from atrophy or from serious arrest in growth. The varicocele of child and teenage years may well require surgical correction under certain conditions described herein.

Anatomy and Physiology

The venous return from the left testis is quite different from that on the right (Figure 1). The right spermatic vein arises from the arborization of veins surrounding the testis and its contents, becoming a single conduit just above the internal inguinal ring. It enters the vena cava at an acute angle, before the entrance of the renal vein. Its blood flow is thus added to the larger vena caval stream, which provides little or no resistance at its entrance into this main system. In contrast, the left internal spermatic vein, after a similar arborization in the scrotum, courses parallel to the vena cava and enters the left renal vein at right angles to flow. In the upright position this anatomical arrangement produces an increased pressure gradient on the left. Any failure in the venous valvular action produces dilatation of the dependent vascular bed to the point that stream is slowed and at times reversed, allowing renal venous blood to enter the dependent spermatic system. When the patient is supine, the enlarged vessels may not be felt in the scrotum, or are felt as collapsed cords. When the patient is standing, the veins are rapidly engorged, to the point that the scrotal plexus can be felt as very large cords. The added weight of the venous blood may lead to scrotal enlargement on the left side.

The physiologic effects on the testicle itself (possibly atrophy or testicular arrest) and on both testes (possibly infertility) must still be considered largely as conjecture. Yet it is conceivable that a change in scrotal temperature, more pronounced on the left than on the right, occasioned by the warmer retrograde flow from within the body cavity, would be influential. Such effect would be accentuated by the superimposed stasis of venous blood in the dilated system. It is well accepted that a difference in temperature will impair spermatogenesis in humans. Lipshultz and Corriere noted that their infertile patients' testes are measurably smaller than those of the fertile controls and they suggest that warmth is the limiting agent.[1]

Patients and Methods

Our patient group consists of 30 boys and young men between the ages of 8 and 18 years. One of them, an 8-year-old boy, is, we believe, the youngest patient with varicocele yet reported. The presenting complaints were as follows: scrotal ache, usually after exercise (nine patients); scrotal mass—to be identified (seven patients); varicocele (eight patients); enuresis, proteinuria, meatitis (six patients).

We graded the varicoceles as follows:

Grade 1: Veins clearly palpable as cords with the patient in the upright position.

Grade 2: Massive distention of the venous system in the scrotum.

The comparative sizes of the testes judged by gross palpation were recorded as follows:

Grade 1: The testicle clearly smaller than its counterpart.

Grade 2: The testicle ¼ or less the size of the right one.

In all cases the venous distention subsided with the patient in the supine position. Semen quality was not studied. An excretory urogram (IVP) was routinely obtained for diagnostic evaluation.

During the same period, 88 adults with infertility and varicocele were evaluated and surgically treated. Com-

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parison of observations of this group with the teenage group aided us in our study of this lesion.

Surgical Indications

Interruption of venous flow via the internal spermatic veins is the goal of corrective operation. The venous return from the testis is not impaired, for it is then completely and safely shunted via small collateral vessels, entering the deep circulation below the level of the surgical interruption.[2] Direct scrotal approaches have long been condemned because of the severe complications from bleeding and the inability to locate each venous channel. If the venous return via the spermatic vein or veins is eliminated, the operation is uniformly successful. After several months, the veins can be palpated as collapsed, thin cords when the patient is standing.

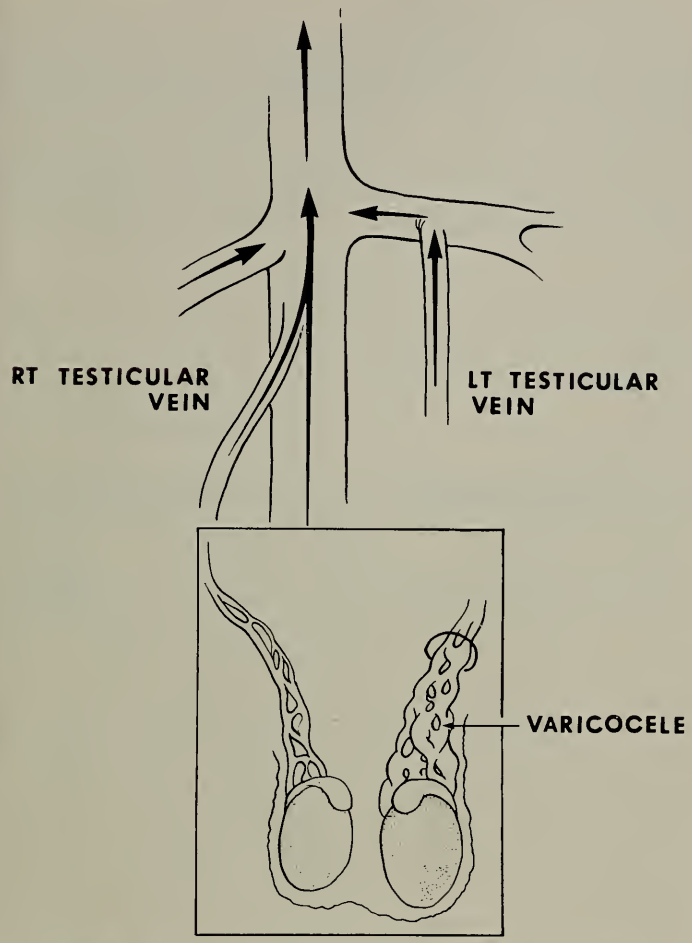

Figure 1.—Venous return from left and right testes.

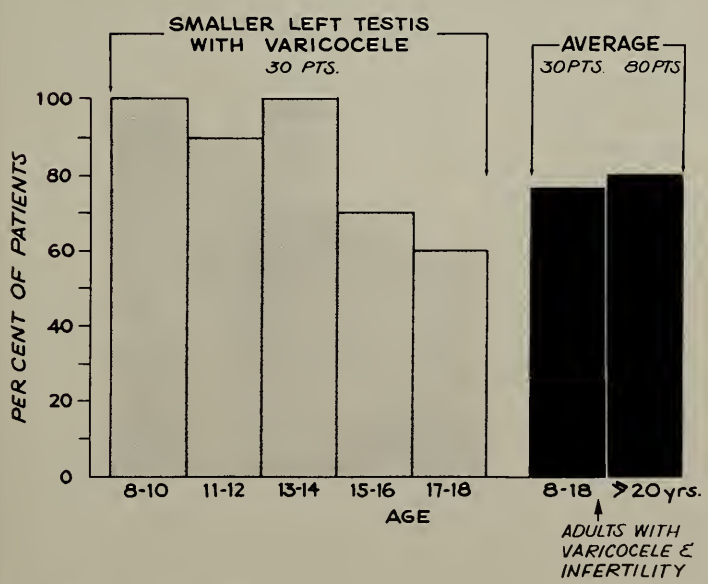

Figure 2.—LEFT, Association of left varicocele with smaller left testis in youth. RIGHT, Incidence of smaller left testis in boys with varicocele and in adults with varicocele and infertility.

In this series, we have limited our surgical correction to (1) those patients whose symptoms are believed to arise from the varicocele regardless of the grade of varicocele or of testicular size; (2) those with grade 2 varicocele, regardless of testicular size, and (3) those with a clearly smaller left testicle regardless of the degree of varicocele size.

Results

The grades of varicocele and of testicular size are given in the Patients and Methods section. Figure 2 plots the percentage of smaller left testes with respect to age (8 to 18 years old when the child was first seen); these figures are then compared with the findings in adults. In 77 percent of the young patients the left testis was demonstrably smaller than the right one (Figure 2). In 10 percent there was what we consider to be an advanced form of growth arrest, the left testis being not more than a fourth the size of the right one. Though the smaller testis tended to be softer in consistency, this was not a uniform finding. No consistent relationship of the varicocele grade to the degree of testicular growth arrest was discovered; neither was there any correlation between symptoms (scrotal aches) and grade of varicocele or testicular size.

The incidence of growth arrest was highest in the 8 to 14 age group, amounting to almost 100 percent. This suggests that the earlier the varicocele develops the greater its effect on the growing testis.

Discussion

Previous studies are few and limited. Two, one from Denmark[4] and one from Belgium,[5] suggest that the varicocele first appears when the boy is between the ages of 10 and 14 (incidence 2 percent to 11 percent). In the report from Belgium, involving more than 4,000 adolescents and college students, the investigators noted a smaller left testis 34 percent of the time with a grade 2 varicocele, and 81 percent of the time with a grade 3 varicocele. The authors concluded that subjects with varicocele grade 2 or 3 are at risk for disturbances in fertility. Although Russian investigators have been interested in the pathogenesis of childhood varicocele for a long time,[6,7] and have a large experience in its surgical correction, they have paid little attention to testicular morphology.

Lipshultz and Corriere[1] made careful measurements

of testicular size of patients having a combination of infertility and varicocele. In their control patients (fertile, no varicocele) they found that the normal testes were symmetrical, but in the presence of varicocele, a smaller left testis was likely to be found. They further suggested that often both testes are smaller than normal when a left varicocele exists.

In our series, 82 percent of our adult patients who have both infertility and varicocele have a smaller left testis. Of the youth group, 77 percent had a smaller left testis associated with a varicocele (Figure 2), a figure extremely close to that in the adults. We noted a small left testis in 20 percent of our adult infertility group and serious arrest in 10 percent of our young patients. The loss of testicular mass in the 8 to 13 age group is striking, which suggests that in these years of rapid growth varicocele has its most damaging effects and perhaps its greatest requirement for surgical correction. A surprising result after corrective operations was *catch up* growth of the smaller testis in two patients, to the point that left and right testes were equal in size and consistency two years later.

Conclusions

From this study of 30 boys with varicocele, we conclude the following: (1) The appearance of a varicocele presumably is related to the physical changes occurring with puberty since rarely does a varicocele appear before puberty. (2) There is no evidence that the varicocele necessarily increases in size with age. (3) The size of the varicocele bears no consistent relationship to left testicular size at presentation. (4) The earlier the varicocele appears the more likely the chance of arrest of testicular growth.

Efforts at detecting the presence of varicocele by examining the genitalia of young male patients in the upright position are worthwhile because of the possible relationship between varicocele, small testis and lowered fertility. Surgical correction is recommended when the varicocele is very large, the left testis is appreciably smaller than the right or there is scrotal discomfort.

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Computerized Tomographic Scanning in Cases of Dementia

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In assessing the clinical value of computerized tomographic (CT) scanning in elderly patients with dementia, only one of 100 patients with dementia of insidious onset and no other abnormal neurologic signs was found to have a potentially treatable disorder. In a second group of 100 patients with dementia of abrupt onset or with additional abnormal neurologic signs, 12 were found to have a lesion that potentially required medical or surgical intervention. We conclude that a subgroup of patients with dementia, representing about a third of demented patients in our hospital, are unlikely to benefit from CT scanning.

With the rapidly increasing number of elderly persons in the population there has been a corresponding increase in the incidence of dementia. Given the extent of this problem it is incumbent on the medical establishment to develop a cost-effective plan for the workup of patients who have dementia. In most communities in the United States computerized tomographic (CT) scanning is considered a requisite procedure for the evaluation of dementia. Yet it has not been proved that a CT scan is of value in all cases of dementia. In our study we set out to identify those patients who are most likely to benefit from a scan.

Lipowski[1] lists nearly 70 causes of dementia, of which about 20 are considered treatable. It has been estimated that from 10 percent to 15 percent of demented persons have a treatable disorder.[2] Of these conditions, only intracranial masses and obstructive hydrocephalus are readily diagnosed by CT scanning. The other disorders can be identified through clinical findings, blood tests and electroencephalography.

As of this writing there have been five studies published that attempt to estimate the incidence of specific causes in patients who have dementia.[3-7] These studies involved a total of 361 patients. Of these patients 5.2 percent had an intracranial mass, only about half of which were potentially resectable. Another 6.4 percent of the patients had normal-pressure hydrocephalus. Unfortunately, in none of these studies were clinical findings correlated with the diagnosis.

The presence of an intracranial mass can usually be suspected from the history or from physical findings, or both. Relevant historical clues include a history of carcinoma, rapid deterioration in mental state, head trauma and seizures. Focal cerebral signs and papilledema are important physical findings.

Obstructive hydrocephalus may be subdivided into two types. *Noncommunicating* hydrocephalus occurs when there is obstruction to the outflow of cerebrospinal fluid from the ventricles into the subarachnoid space. It is usually associated with signs of increased intracranial pressure such as nausea, vomiting and papilledema. In *communicating* hydrocephalus the ventricular cerebrospinal fluid communicates freely with the subarachnoid space. Many of these patients have normal intracranial pressure, hence the term normal-pressure hydrocephalus.[8-10] The condition classically presents with the triad of dementia, urinary incontinence and gait disturbance (ataxia or apraxia). Most patients who have normal-pressure hydrocephalus have a gait disturbance preceding or concurrent with the onset of noticeable dementia.[11] Some patients improve remarkably following ventricular shunting. However, those patients with normal-pressure hydrocephalus who do not have a gait disturbance or urinary incontinence are unlikely to benefit from ventricular shunting.[11,12]

In this study we attempted to delineate criteria for the identification of patients in whom the CT scan is unlikely to provide clinically useful information.

Patients and Procedures

Reports of CT scans in the neuroradiology section of the Long Beach Veterans Administration Medical

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From the Psychiatry Service, Veterans Administration Medical Center, Long Beach, California. (The views expressed in this article are not intended to represent the official position of the Veterans Administration.)

Submitted, revised, August 27, 1982.

Reprint requests to James T. Dietch, MD, 12621 Lewis #33, Garden Grove, CA 92640.

TABLE 1.—*Criteria for Selecting Patients With Dementia Who Are Unlikely to Benefit From Computerized Tomographic Scanning*

Dementia for at least one month
No head trauma in the week preceding change in mental state
Gradual onset (less than 48 hours) of changes in mental state
No history of malignant tumor
No history of cerebrovascular accident
No history of seizures
No history of urinary incontinence
No focal cerebral signs
No papilledema
No visual field defects
No apraxia or ataxia of gait

TABLE 2.—*Computerized Tomographic Scan Diagnoses in Patients With Dementia Who Met Criteria (N=100) Compared With Those With Dementia Who Did Not (N=100)*

Diagnoses	*Criterion Patients*	*Comparison Patients*
Normal*	13	15
Cerebral atrophy†	77	54
Infarct (single or multiple)	9	19
Neoplasm	1	6
Normal-pressure hydrocephalus	..	2
Subdural hematoma	..	1
Subdural hygroma	..	1
Intracerebral hematoma	..	1
Intraventricular hemorrhage	..	1
TOTAL	100	100

*Within normal limits for patient's age.
†Patients in whom cerebral atrophy is the only diagnosis.

Center are filed according to Social Security number. The records of patients at least 50 years of age with clinical findings suggestive of dementia were reviewed.* Only patients who had had a neurologic examination were selected. In most patients this examination was done by an attending neurologist or neurology or internal medicine resident. Most CT scanning for the diagnosis of dementia is requested for patients on the medicine and neurology services.

The first 100 patients who met the inclusion criteria listed in Table 1 were placed in the "Criterion" group. The criteria were selected to exclude patients likely to have an intracranial mass or obstructive hydrocephalus. About a third of all patients who had CT scanning for dementia met the inclusion criteria. A "Comparison" group was formed from the first 100 patients who failed to meet one or more of the inclusion criteria. All CT scans were done using infusion of contrast material except when an intracranial hemorrhage was thought to be present. The CT scanner was an Artronics fourth-generation fan-beam head scanner. All CT scans were interpreted by an experienced neuroradiologist.

*Apostolos Alekoumbides, MD, Staff Neurologist, provided technical assistance in the formulation of methodology.

Results

The CT scan diagnoses of the 200 patients studied are given in Table 2. Of the "Criterion" patients only one had a potentially treatable disorder—an astrocytoma. Although this patient was treated with radiation therapy, he died within a month after the date of his CT scan. Of the "Comparison" patients, ten were found to suffer an intracranial mass and two had normal-pressure hydrocephalus. In contrast to previously published studies[2] our "Comparison" sample had a higher incidence of intracranial masses and a lower incidence of normal-pressure hydrocephalus. The difference in frequency of potentially treatable lesions between the "Criterion" and "Comparison" groups was significant at the P less than .005 level ($\chi^2 = 8.24$, $df = 1$).

Discussion

Of the 100 Criterion patients, none had a reversible lesion. Although the patient with an astrocytoma met all of our inclusion criteria, his history showed the onset of severe headaches two months before diagnosis. In view of his history we would now add to our inclusion criteria the absence of a recent onset of severe headaches. It should be noted that in most communities the recent onset of severe headaches (even in the absence of dementia) would be reason enough to do a CT scan.

A majority of patients in both the Criterion and Comparison groups were noted to have cerebral atrophy, a finding suggestive of Alzheimer's disease. It might be argued that CT scanning is a useful procedure for establishing a definitive diagnosis, even if it be an untreatable disorder. Yet the finding of cerebral atrophy does not provide a definitive diagnosis. Up to 20 percent of normal persons without evidence of dementia show signs of cerebral atrophy.[13] Thus, overreliance on the findings of a CT scan in cases of dementia may lead to serious diagnostic errors.

In patients who meet our inclusion criteria, electroencephalography may be a more useful procedure. Due to the fact that a significant percentage of our patients did not have an electroencephalogram, we are unable to provide empirical support for this idea. Other studies have shown, however, that most treatable causes of dementia are associated with prominent electroencephalographic abnormalities.[14] This is particularly true for localized lesions that have grown large enough to produce signs of dementia.[15]

In conclusion, our data indicate that patients who meet our inclusion criteria are unlikely to benefit from CT scanning—that is, their course and treatment are not improved by the findings on a CT scan. In addition to the criteria listed in Table 1, we would now add "absence of recent onset of severe headaches." About a third of demented patients in our hospital meet these criteria. Because our data are retrospective, they represent findings that need further support from prospective

studies. Undoubtedly our criteria will not identify all patients who are unlikely to benefit from CT scanning, but "diagnosis at any cost" may no longer be feasible.

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Articles to Read in Other Journals

Meniscectomy—Editorial Comment

Nicholas JA
American Journal of Sports Medicine
10:357-359, No 10, 1982

DISCIPLINES: Orthopedic Surgery

READABILITY: Very good

The author presents an enthusiastic discussion of arthroscopic meniscectomies and the advantages thereof. He does qualify his enthusiasm with the following statement: "The ultimate of arthroscopic meniscectomy may not be known for 10-20 years." The editorial comment by James A. Nicholas, MD, at the end of the paper is worthy of being read. This editorial comment raises questions concerning the author's objectivity. Details of meniscectomy techniques are not in the paper. It is noted that the patient population is heavily slanted toward students. Criticism of student recovery versus Workers' Compensation patient's recovery is made. Some of the risks of arthroscopic surgery are discussed, something which arthroscopists tend to ignore. Dr Nicholas' comments are important to orthopedists and to primary physicians advising their patients concerning arthroscopic surgical procedures versus conventional arthrotomy. Dr Nicholas states that the arthrogram at times can better determine anterior detachment of the meniscus than the arthroscope. He makes a plea for honesty in reporting facts concerning open and closed meniscectomy.

DUANE M. KLINE, MD
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Medical Progress

Treatment of Diabetes With Insulin

From Art to Science

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Improved understanding of the physiology and pharmacokinetics of insulin and new therapeutic devices allow an increasingly rational approach to the treatment of diabetes with insulin. The complexity of the regimen necessary for successful control of blood glucose levels depends largely on a patient's relative deficiency of endogenous insulin. Patients initially treated successfully with single or twice-a-day injections often, as the amount of endogenous insulin dwindles, progress to a complex regimen more closely mimicking normal patterns of secretion. Self-monitoring of blood glucose values and attention to many simple factors affecting absorption of insulin and glycemic behavior strongly enhance the success of all regimens. Patients and physicians must collaborate to plan and execute individualized therapeutic regimens using available tools to the best advantage.

Insulin is a remedy primarily for the wise and not for the foolish, be they patients or doctors.

ELLIOTT JOSLIN, 1928[1]

Insulin has now been used some 60 years for treating diabetes. Given that span one might expect clear guidelines for selection and modification of regimens for administering insulin to have evolved. This has not happened; the clinical use of insulin remains largely an empirical art. Clinicians generally use regimens with which they are comfortable, matching them to subgroups of patients by rather arbitrary guidelines. In the best circumstances such beginnings lead, through trial and error, to a successful outcome for each patient. Unfortunately, less desirable results are also common. Studies prospectively comparing various regimens are few, and most textbooks are surprisingly vague on the best way to approach treatment of any given patient.

Several converging forces are bringing this state of affairs to an end. Recent information has done much to answer the question of whether hyperglycemia directly causes tissue changes. Most studies to date show that worse hyperglycemia does indeed correlate with worse diabetic complications.[2-5] The National Institutes of Health are planning a large prospective trial of close glycemic control versus "conventional" treatments that may show more conclusively whether or not excellent control can prevent or minimize the long-term effects of diabetes. At the same time our patients grow ever more willing to invest time, money and energy to achieve good glycemic control. Finally, technical advances of the past few years have given us better therapeutic tools and better understanding of the physiologic process we wish to mimic by the administration of exogenous insulin. Thus, even without fully successful results from β-cell transplants or artificial pancreases, we can now with the collaboration of our patients choose, evaluate and modify insulin prescriptions more rationally and with greater hope of success. Following is a description of a way to approach this task.

Improved Understanding of Endogenous Insulin Secretion

Deficiency of endogenous insulin is the leading metabolic determinant of glycemic instability in diabetes.[6,7] Patients who have noninsulin-dependent diabetes all retain some capacity to secrete pancreatic insulin, though secretion is imperfectly regulated or inadequate to meet increased needs. In some patients this capacity dwindles with time.[8] Many patients with noninsulin-dependent diabetes have prominent though transient worsening of glycemic control during preg-

Refer to: Riddle MC: Treatment of diabetes with insulin—From art to science (Medical Progress). West J Med 1983 Jun; 138:838-846.

From the Diabetes Clinic, Section of Metabolism, Department of Medicine, The Oregon Health Sciences University, Portland.

Submitted, revised, December 16, 1982.

Reprint requests to Matthew C. Riddle, MD, Director, Diabetes Clinic, Head, Section of Metabolism, Department of Medicine, The Oregon Health Sciences University, Portland, OR 97201.

TABLE 1.—*Examples of Commonly Used Insulin Preparations*

Rapidity of Action	*Conventional/Improved (10 ppm Proinsulin)*	*Source*	*Purified (10 ppm Proinsulin)*	*Source*
Fast	Iletin I, Regular (Lilly)	Bovine-porcine	Iletin II, Regular (Lilly)	Porcine
	Insulin (Squibb-Novo*)	Porcine	Actrapid (Squibb-Novo)	Porcine
			Velosulin (Nordisk-USA)	Porcine
Medium fast ...	Iletin, Semilente (Lilly)	Bovine-porcine	Semitard (Squibb-Novo)	Porcine
	Semilente (Squibb-Novo)	Bovine	Mixtard (Nordisk-USA)	Porcine
Intermediate ...	Iletin, NPH (Lilly)	Bovine-porcine	Iletin II, NPH (Lilly)	Porcine
	Iletin, Lente (Lilly)	Bovine-porcine	Iletin II, Lente (Lilly	Porcine
	NPH (Squibb-Novo)	Bovine	Protaphane (Squibb-Novo)	Porcine
	Lente (Squibb-Novo)	Bovine	Monotard (Squibb-Novo)	Porcine
			Lentard (Squibb-Novo)	Bovine-porcine
			Insulatard (Nordisk-USA)	Porcine
Slow	Protamine, Zinc & Iletin (Lilly)	Bovine-porcine	Protamine, Zinc & Iletin II (Lilly)	Porcine
	Iletin, Ultralente (Lilly)	Bovine-porcine	Ultratard (Squibb-Novo)	Bovine
	Protamine, Zinc & Iletin (Squibb-Novo)	Bovine		
	Ultralente Insulin (Squibb-Novo)	Bovine		

ppm = parts per million

*The Novo and E. R. Squibb companies have recently merged.

nancy, periods of weight gain or use of drugs opposing the action of insulin. Variably diminished responsiveness of tissues to insulin is characteristic of noninsulin-dependent diabetes[9] and the relative roles of abnormal secretion and abnormal action of insulin in the pathogenesis of this disorder are currently debated.[10]

Patients who have insulin-dependent diabetes, which appears to be a more homogenous classification, are believed to suffer an acute injury to β-cells, favored by genetic predisposition but triggered by an external factor, possibly a virus.[11] The initial injury leads to moderate or severe lack of insulin but may be followed by a partial recovery, the "honeymoon" phase. Subsequent injury possibly mediated by autoimmune mechanisms further impairs insulin secretion. In most cases a complete lack of endogenous insulin ensues within several years. This pathogenetic sequence matches and to some extent explains the clinical pattern physicians have observed for years in patients with this type of diabetes.

Patients with abnormal glycemic regulation who retain some endogenous insulin typically have both qualitatively and quantitatively abnormal responses of insulin to meals or glucose.[12] The "acute phase" response of secretion in the first several minutes following intravenous injection of glucose is blunted or absent, whereas the "second phase" response may be more normal. The rise of the insulin level in plasma after glucose is taken orally is delayed and prolonged. This pattern may in part result from insensitivity of the β-cell to glucose despite retention of responses to other stimuli. Activation of the sympathetic nervous system by stress[13] or the administration of β-adrenergic blockers,[14] thiazide diuretics,[15,16] phenytoin[17] and possibly calcium channel blockers[18] may further impair secretion. Better glycemic control in some cases improves the responsiveness of the β-cell.[19,20]

The clinical relevance of these observations lies in the recognition that the relative insulin deficiency in both noninsulin-dependent and insulin-dependent diabetes commonly is progressive and may wax and wane both with systemic stresses such as obesity and pregnancy and with variations in β-cell competence. This awareness helps in planning a strategy for treatment and preparing a patient for what lies ahead.

The normal pattern of insulin secretion in humans is now well defined. Daily secretion in adults of average size and normal adiposity is in the range of 30 to 40 units.[21-23] The liver extracts about half the insulin secreted on the first pass.[23] About half the daily output of insulin provides a basal level of circulating insulin during the span of time between meals. The remaining half is secreted in response to meals, a surprising amount—about 15 percent to 20 percent of the daily total—being secreted at breakfast time. The greater requirement for insulin in the morning precedes breakfast.[24,25] An increase in basal insulin secretion is, at least in some persons, necessary to maintain normal plasma glucose level from about 4 AM through midmorning,[25] possibly due to the effects of catecholamines, cortisol or growth hormone. When endogenous insulin is lacking, injected insulin must mimic the normal pattern to bring the glucose to normal levels. An obstacle to matching the normal pattern perfectly is the difficulty of delivering exogenous insulin to the portal circulation. Insulin given subcutaneously enters the systemic rather than the portal circulation, so the usual ratio of portal-to-systemic concentrations is not reproduced.

Recent Technical Improvements

Insulins

In the past few years, insulins of very high purity—that is, containing less than 10 ppm of noninsulin materials—have been marketed.[26-28] Using purer insulins reduces the incidence of local and systemic allergy and of lipoatrophy and scarring at the site of injection.[29-32]

The daily dose required is often less and, while not yet proved, it has been suggested that purer insulins are more rapidly and consistently absorbed. Also, with the entry of two European manufactures, Novo (recently merged with E. R. Squibb & Sons, Inc) and Nordisk (Nordisk-USA), into the American market, a wider selection of preparations has become available. We can now choose between several degrees of purity of bovine-porcine mixtures and pure bovine or pure porcine insulins, and among fast-acting, medium-fast-acting, intermediate-acting and slow-acting insulins. Many of the preparations available are shown in Table 1. This variety can lead to confusion but it also allows selection of the precisely appropriate insulin for each situation.

Syringes and Pumps

A glass syringe that needs repeated sterilization has been superseded by inexpensive, accurate and disposable plastic syringes with very sharp needles.[33,34] These are more convenient and less painful to use and consequently are better accepted by patients. Furthermore, several commercial models of mechanized infusion pumps are now available.[35,36] These pumps are worn attached to or under clothing and deliver insulin into a subcutaneous space. More sophisticated designs are being tested, including ones to be implanted under the skin.[37,38] The present generation of pumps includes only "open-loop" models that lack a glucose sensor and therefore require frequent adjustments by a wearer. Continuous delivery of insulin offers real advantages, the greatest being avoidance of variable absorption of intermittently injected insulin. But the devices now in use also have disadvantages, including cost ($1,000 to $2,000), complexity of operation, bulkiness of the pump and delivery tubing and the risk of inflammation and infection at the site of infusion.[39] Nor are they foolproof, as ketoacidosis and hypoglycemic coma are not always prevented by their use.[40] A compromise between conventional injection and continuous infusion by a pump has been proposed, using a butterfly needle or cannula placed subcutaneously as a portal for frequent manual injections.[41,42]

Devices for Monitoring Glucose Content

Traditional methods (for example, Clinitest, Diastix, Testape) for monitoring urine glucose content are now commonly supplemented or replaced by measurement of capillary-blood glucose concentration.[43-45] Two technical advances have made this possible. First is the construction of inexpensive spring-loaded devices (for example, Autolet, Autoclix) bearing small, sharp lancets that puncture the fingertip nearly painlessly to obtain capillary blood. Second is the development of reliable glucose-oxidase reagent strips for measuring the glucose content in blood (such as Chemstrips bG, Dextrostix, Visidex). These strips can be read against a color chart, but some persons, for example, those who have poor vision, prefer to use a photoelectric cell device (Glucometer, Stat Tek, Glucoscan) for reading color development. Both visual and photocell measurements are accurate enough for making clinical decisions.[46] Using these methods, many patients willingly test blood glucose level four or even more times a day during educational periods or times of poor control. Self-measurement of blood glucose levels has proved a powerful tool for learning the feat of balancing food, exercise and amount of insulin to regulate blood glucose content.

Assay of glycosylated hemoglobin, which reflects glycemic control in the preceding one to three months, adds yet another dimension.[47,48] This procedure objectively assesses a patient's success over an extended period and may suggest errors in measuring glucose levels by a patient, falsification of data or unrecognized hypoglycemia in patients thought by other indicators to have acceptable control. It is especially likely to yield additional information for those patients who have insulin-dependent diabetes mellitus. Both chromatographic and colorimetric methods of assay are available. The former are most widely used but more vulnerable to artifacts related to recent glycemic behavior, storage of samples, variant hemoglobins and azotemia.[46]

Improved Understanding of Absorption of Injected Insulin

The rate of absorption of subcutaneously injected insulin is determined in part by the type of insulin used but also by other factors. The subcutaneous sites commonly used have different patterns of absorption: for example, fastest in the abdomen, slowest in the thigh and intermediate in the upper arm.[49-52] Physical activity speeds absorption,[51-54] especially when the limb bearing the depot of insulin is exercised. Ambient temperature also has an effect, presumably related to dermal blood flow, with absorption of insulin being quicker in a warm environment[55] or following a hot bath.[52] Some persons appear to have insulinase activity in the skin, degrading injected insulin and causing a syndrome imitating cellular resistance to insulin.[56,57] In such persons insulin given intravenously acts normally. Finally, there are individual differences in rate of absorption apparently unrelated to any of the above factors.[50] Some persons absorb zinc suspension (lente) or isophane suspension (NPH) insulin rapidly, with peak action between four and eight hours, whereas others have slower absorption, with the peak coming later than 12 hours after injection.[58] Knowledge of these variables clarifies otherwise mystifying clinical events and permits manipulation of the use of insulin to clinical advantage.

Available Insulin Regimens

The less endogenous the insulin, the more elaborate is the injection regimen required to duplicate physiologic needs and achieve good glycemic control. The relationship between insulin reserve and treatment required is shown in Figure 1. It is characteristic of patients who have insulin-dependent diabetes and common with noninsulin-dependent diabetic patients for a progressively more sophisticated regimen to be required as relative insulin reserve dwindles. The time span be-

TABLE 2.—*Summary of Insulin Regimens*

Insulin Regimen and Speed of Action	*Time of Day of Injection*			
	*Breakfast (units)**	*Lunch (units)*	*Supper (units)*	*Bedtime (units)*
Single dose				
Intermediate only	I (100)			
Intermediate plus fast	I/F (70/30)			
Two dose				
Morning mixed, afternoon fast	I/F (50/25)		F (25)	
Morning and afternoon "split-mixed"	I/F (45/25)		I/F (15/15)	
Complex				
Three injections	I/F (30/15)		F (25)	I (30)
Four injections	F (20)	F (20)	F (20)	I (30)
Continuous subcutaneous infusion	Infusion (40-60) plus F(10-20) with each meal			

I = intermediate; F = fast

*The proportions of the total daily dose typically given as each component of each dose are shown in parentheses. Individual patients may of course require distributions quite different from those shown. In practice, dosage must always be adjusted to individual needs as judged by results of glucose tests.

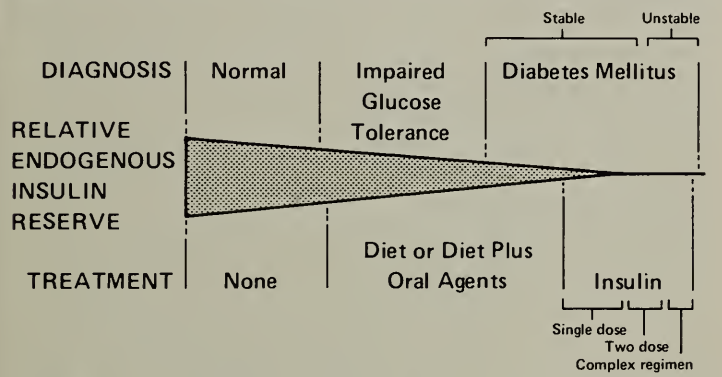

Figure 1.—A simplified diagram showing the relation between relative endogenous insulin reserve, the resulting type of glycemic abnormality and the therapeutic regimen likely to be effective. A patient may progress from left to right with gradually diminishing insulin reserve, progressively more labile plasma glucose level and need for an increasingly refined therapeutic regimen.

tween onset of diabetes and total absence of insulin in insulin-dependent diabetes typically varies from several weeks to several years. Patients who have the noninsulin-dependent type who suffer progressive loss of insulin reserve have a slower process that may extend for several decades. In either case the simplest regimen, a single injection, may suffice initially, while the future need for multiple doses should be anticipated. Of course, other factors besides endogenous insulin reserve influence the success of a given regimen. In addition to a patient's zeal in following the plan of treatment, his or her daily schedule, lability of secretion of counterregulatory hormones and pattern of absorption of insulin all in part determine the regimen necessary.

The widely used regimens may be conveniently divided into three groups: single-dose, two-dose and complex regimens (Table 2).

Single-Dose Regimen

The *intermediate* insulins (NPH and lente) were designed to provide action lasting 24 hours from a single injection given in the morning.[59,60] When considerable insulin reserve is present, a single dose of intermediate insulin provides a basal level in plasma, highest during the day, to which secretion of endogenous insulin adds meal-time increments appropriate to the need. Some physicians advocate using *slow* insulins (protamine zinc insulin or extended insulin zinc suspension) for this purpose and describe successful outcomes.[61] A disadvantage of slow insulins is the retention of insulin in the subcutaneous depot, accelerated absorption of which may follow exercise or a rise in ambient temperature. In addition, because each injected dose lasts several days, a change of dosage cannot be made on short notice. Both of these properties of slow insulin lead to episodes of hypoglycemia, especially at night.

The first evidence of failure of a single dose of intermediate insulin given before breakfast depends on the rate of absorption in an individual patient.[58] Persons with slow absorption and prolonged action of intermediate insulins may have daytime hyperglycemia or nocturnal hypoglycemia, or both. When this pattern occurs, the addition of fast insulin to the morning injection with reduction of the dose of intermediate insulin is helpful. Typically, 25 percent to 30 percent of the total dose given as fast insulin in a single morning injection works best. Persons who absorb intermediate insulins rapidly, by contrast, are prone to hypoglycemia late in the morning or in midafternoon and may be hyperglycemic before breakfast. This pattern usually calls for a second dose of insulin. A second dose is also necessary for patients initially treated successfully with a single morning dose of intermediate or intermediate-plus-fast insulin in whom hyperglycemia later develops before breakfast despite continued good control during the day. In this case the difficulty stems not from inappropriate duration of action of injected insulin so much as from declining secretion of endogenous insulin at night.

Two-Dose Regimen

A second dose of insulin is usually given before supper.[62,63] The safest way to begin a two-dose regimen is to add fast insulin at supper while decreasing the morn-

ing intermediate insulin and, if this has not already been done, adding some fast insulin to the morning dose as well. The resulting distribution of insulin often approximates 75 percent in the morning—50 percent as intermediate and 25 percent as fast insulin—with 25 percent given in a dose of fast insulin before supper. This distribution works well for many patients who have insulin-dependent diabetes and are retaining some endogenous insulin and for patients with noninsulin-dependent diabetes that is inadequately controlled on a single injection. Failure of this regimen is usually marked by hyperglycemia before breakfast, requiring the addition of intermediate insulin to the afternoon dose. The distribution of insulin then moves toward 60 percent to 70 percent in the morning, two thirds (40 percent to 50 percent of the total) as intermediate insulin, and 30 percent to 40 percent at supper split equally (15 percent to 20 percent) between intermediate and fast insulin. Breakfast, lunch, supper and a bedtime snack each coincides roughly with the peak action of one of the four separate doses of insulin in this regimen.

Most persons with negligible endogenous insulin require a regimen of at least this complexity. A major limitation of this distribution is the tendency for the effect of intermediate insulin given before supper to peak around 3 AM, when little insulin is needed, yet be on the wane when the requirement for insulin rises before breakfast. A frequent consequence is persistence of fasting hyperglycemia despite normal or low glucose levels at 3 AM. Repeated nocturnal hypoglycemia, often unrecognized, is not uncommon and can be debilitating.[64] This undesirable pattern requires a more complex regimen.

Complex Insulin Regimens

A few persons with diabetes require a strategy beyond the two-injection regimen. Such persons are virtually without endogenous insulin. Three types of complex regimens can be identified.

Three-injection regimen. Moving the intermediate component of evening insulin from suppertime to bedtime commonly corrects the problems of nocturnal hypoglycemia and persisting fasting hyperglycemia.[65,66] Intermediate insulin given around 10 PM begins to peak between 6 AM and 8 AM when it is most needed. The proportion of the total dose given successfully thus varies considerably. About a sixth (15 percent to 20 percent) of the daily total is a good initial dose, equivalent to the dose of intermediate insulin commonly given at suppertime in the mixed two-injection regimen, but 30 percent or even 50 percent of the total dose is successful for some patients. Typically the distribution of doses in this three-injection plan includes 30 percent to 50 percent of the total as intermediate and 10 percent to 20 percent as fast insulin before breakfast, 10 percent to 20 percent as fast insulin before supper and 15 percent to 50 percent at bedtime as intermediate insulin.

Four-injection regimen. Alternatively, three doses of fast insulin can be given before meals, together with a dose of intermediate insulin at bedtime.[65,67] With this distribution 15 percent to 30 percent of the total dose is given as fast insulin with each meal, and 15 percent to 50 percent as intermediate insulin at bedtime. Because the amount of depot insulin present during the day is less than that with simpler regimens, and because each meal has its own dose of fast insulin, more flexibility of meal timing and size is possible. At the same time, four injections a day are burdensome. Use of an indwelling subcutaneous needle or cannula may make this many injections more acceptable.[39-40]

Continuous subcutaneous insulin infusion. Pump-driven subcutaneous infusion, with boluses at mealtime also delivered by pump, is the most refined regimen currently available.[33,34] The basal infusion necessary varies from 40 percent to 60 percent of the total daily dose of insulin. The remainder is divided into boluses before each meal or snack. Pumps capable of preprogrammed changes in basal infusion rate are available, so an early morning increase in need for basal insulin can be accommodated. Because no subcutaneous depot of modified insulin is present when fast insulin is delivered by continuous subcutaneous insulin infusion, variation in absorption is largely eliminated as a source of difficulty and the timing of meals is optional. Use of continuous subcutaneous infusion does not relieve a patient of the responsibility for planning and administering mealtime doses. Changes in requirement for insulin due to size of meals, illness, medication, menstrual cycle and other factors must still be accommodated by the operator-patient.

Three other complex regimens, omitted from the preceding outline for clarity of exposition, also deserve mention. First, the combination of slow insulin given once or twice a day to provide a basal insulin level plus fast insulin given two, three or four times a day before meals has advocates.[68,69] This strategy is attractive but has the same drawbacks as slow insulin given alone. Second, three or four injections of fast insulin given before meals with no depot insulin is said to be successful for certain patients. The weakness of this regimen is its lack of provision for basal insulin delivery before breakfast. Third, a combination of nocturnal continuous subcutaneous infusion and daytime multiple injections of fast insulin has been proposed.[70]

Choosing a Regimen

Selecting an Insulin Preparation

With so many kinds of insulin now available, selection of species, purity and depot preparation has become problematic. Objective data in the literature are still inadequate to allow fully rational choices. Therefore, decision must be made on a patient-to-patient basis, and each physician must establish personal guidelines.

Eliminating noninsulin peptides reduces manifestations of allergy, and porcine insulin, differing in only one amino acid from human insulin, is less allergenic than bovine insulin with three amino acid substitu-

tions.[27-30] Thus, if cost and availability were not factors, the best grade of porcine insulin would be the preparation of choice. But porcine insulin of purified grade is not in unlimited supply and costs 50 percent to 150 percent more than bovine-porcine mixtures of slightly lesser purity. Furthermore, direct comparisons in various groups of patients of clinical efficacy of bovine-porcine versus porcine and "improved" versus "purified" insulins are few and as yet inconclusive.[71-74] In particular, the possibility that an immune response to enteric peptide hormones present in injected insulins may have adverse effects,[75,76] and the possibility that complexes of insulin and antibodies to insulin may contribute to the vascular complications of diabetes[77,78] are incompletely studied. The following guidelines seem reasonable for the present. For patients for whom cost is not an issue and for those with known allergy to insulin (suggested by generalized or local wheals, delayed swelling or erythema at the injection site, lipoatrophy or scarring, or requirement for more than one unit per kilogram per day), purified porcine insulin is preferable. Patients who have personal or familial history of other allergies, those likely to need insulin only temporarily and those with unsatisfactory glycemic control for no apparent reason are also possible candidates for purified porcine insulin. Those who have no history of allergy and limited finances may try improved conventional bovine-porcine insulin and continue if no difficulties arise.

We are on slightly firmer ground with regard to the choice of sustained-release preparations of insulin. Insulins of both the lente and NPH families have been widely used for years, and their safety and efficacy are proved. Lente insulins have the theoretic advantage of containing no foreign protein as do the protamine-based insulins, but evidence that they are less allergenic is lacking.[79] Bovine-porcine lente insulin has a slightly longer duration of action than NPH,[79] which may at times be advantageous. On the other hand, NPH has advantages, too. It is anecdotally reported that some patients experience less stinging at the site of injection with NPH than with lente insulin. More concrete is the recent finding that mixing NPH and fast insulin results in predictable absorption patterns similar to those when the two are given simultaneously but separately, whereas mixtures of lente and fast insulin yield variably altered patterns.[50,52,60] Thus, when intermediate insulin is given alone there is little reason to prefer either lente or NPH to the other; but when intermediate and fast insulin are mixed, NPH may be preferable.

Because of the foregoing, there is a growing tendency to select purified porcine insulins, fast and NPH, when starting insulin treatment. At the same time, many patients currently use improved bovine-porcine insulins and insulins in the lente series with success, and there is at present no pressing reason for them to change. Once preparations of insulin are selected, a patient is well-advised to shop for the best price because cost varies widely between brands and pharmacies, and the expected increase in marketing competition may yield bargains.

Selecting a Starting Regimen

Assessment of a patient's probable insulin reserve should precede the choice of a therapeutic regimen. In theory, assay of the plasma C-peptide level, either fasting or after administration of a stimulus to secretion, to quantify insulin reserve might help make clinical decisions.[79,80] In practice, the value of this procedure has yet to be established. Thus, the assessment must at present be clinical. The following factors favor extensive insulin reserve: obesity; onset at age older than 40; recent onset; lack of ketosis, and the presence of a stressful illness or the use of corticosteroids, thiazide diuretics, phenytoin or β-adrenergic blockers at the time of onset. Attention to these factors usually allows correct assignment of patients to one of three regimens:

1. *Substantial endogenous insulin:* single injection.
2. *Some endogenous insulin:* two injections.
3. *Little or no endogenous insulin:* complex regimens.

Most patients older than 40 years who have newly diagnosed diabetes requiring insulin fall in the first group, as do some younger persons in the first months of typical insulin-dependent diabetes mellitus. Many patients who have this type of diabetes for more than a year and many who have noninsulin-dependent diabetes for more than ten years fall in the two-injection group. Most persons who have insulin-dependent diabetes for more than five years need a complex regimen for close regulation of glycemia.

Patients expected to do well with a single injection can be started on a regimen of 10 units of intermediate insulin, the dose to be increased gradually. Patients expected to need two injections should be started with or switched to this regimen. The total dose required for adults taking two or more injections is usually in the range of 30 to 50 units per day, but initial recommendations should be conservative. A slender 20-year-old man with hyperglycemia progressive over one year might thus start with 10 units intermediate and 5 units fast insulin in the morning and 5 units fast insulin before supper, with gradual increments as needed during the next week or two. Patients expected to need complex regimens generally have had diabetes and have used insulin for years. The task for this group is rearranging an established daily dose rather than newly starting on insulin therapy. However, with recent findings supporting the notion that early aggressive treatment may prolong residual islet cell function in cases of insulin-dependent diabetes,[81] there may be reason for many patients to move more swiftly than has been customary from two injections to a complex regimen.

Fine Tuning of the Regimen

The pattern of injections is by no means the only variable that can be adjusted to improve control of

glycemia. Meal pattern, timing and composition can be manipulated, too, and many patients prefer changes of food to changes of insulin. Timing and nature of physical activity also can be changed to meet the demands of glycemic control. High glycemic peaks after meals can often be blunted by reducing calories or simple sugars in a meal, or by exercising before or after the meal to speed absorption of insulin. Similarly, a systematic tendency toward hypoglycemia at a given time of day can often be remedied by adding a snack or decreasing activity at that time. The type of insulin or the site of injection can also be changed strategically. Erratic glycemic behavior without other apparent cause sometimes occurs coincident with inflammation at the injection site. Switching to less allergenic insulin is reasonable in such cases and often seems to improve results. Consistent but undesirably rapid or slow onset of insulin action calls for change to a different insulin or to sites of injection known to favor slower or faster absorption. Thus, a person who has insulin-dependent diabetes with moderate hyperglycemia before breakfast on a two-injection regimen, with the second dose given in the abdomen, may have more success if the second dose is given instead in the thigh, from which absorption is slower. Finally, self-monitoring of blood glucose content and education on factors affecting glycemic stability help a patient make appropriate small changes of insulin, food or exercise to match changes in daily routine, yielding better success with a given insulin regimen.[65,82] Many patients who have all but given up hope of achieving acceptable glycemic control are in time able to attain their goals by attention to these conservative measures, without changing the pattern of administration of injection.

Advancing the Regimen

When other methods fail to achieve the desired level of control, a more refined insulin regimen should be considered. When the rationale is made clear, many patients previously reluctant to take more injections will accept the necessary changes. Reducing the total daily dose by about 10 percent is usually wise, and an injection at a new time should be started at a modest dose. For example, a patient going from a single morning dose of 28 units of intermediate with 10 units of fast insulin to a two-injection plan might most safely start with 24 units of intermediate insulin with 6 units of fast insulin in the morning and 4 units of fast insulin before supper. Similarly, a patient taking 20 units intermediate with 8 units fast insulin before breakfast and 6 units of each type before supper might, when switching to a three-injection plan, start with 18 units intermediate and 6 units fast insulin before breakfast, 6 units of fast at supper and 6 units of intermediate insulin at bedtime. Monitoring the capillary-blood glucose level allows further adjustment of each dose.

When a two-injection regimen proves unsatisfactory, choosing the complex regimen to follow presents some problem. There is strong pressure from patients, advertisements, manufacturers' representatives and many physicians to go directly to continuous subcutaneous insulin infusion. Numerous but mostly uncontrolled studies have shown that continuous subcutaneous infusion can achieve good or excellent control much of the time.[83-85] Some studies directly comparing continuous subcutaneous infusion with optimized conventional regimens show better long-term results with continuous subcutaneous infusion.[86,87] Skillful use of three or four injections, however, has been reported by other groups to achieve equally or nearly equally successful control.[67,88,89] Long-term prospective comparisons of the several methods, using a crossover design so that each subject experiences each treatment method, are sorely needed.

The study of Schiffrin and Belmonte,[67] perhaps the best to date, shows the issues and problems we face. In all, 20 subjects with insulin-dependent diabetes mellitus were enrolled in a year-long protocol comparing continuous subcutaneous insulin infusion with a four-injection regimen, using a six-month/six-month crossover design. Four persons dropped out. The 16 remaining subjects showed dramatically improved control on both experimental regimens in comparison to their previous experience on one- or two-injection regimens. No clear advantage of one test regimen over the other was apparent. After the study, two subjects chose to return to their previous mode of treatment and of the other 14, 7 each chose continuous subcutaneous infusion or four injections. Later evaluation of these groups showed that continued excellent control was achieved in both groups only by persons who continued to measure capillary-blood glucose level more than twice a day.[90] From this and other studies, it appears that patients' attention to the less dramatic aspects of management and acceptance of whatever complex regimen is chosen may be the most critical determinants of long-term success.

For the present it seems wise to introduce all patients requiring a complex regimen to a three- or four-injection method before a trial of continuous subcutaneous insulin infusion. Many patients are likely to achieve satisfactory control and choose to continue thus. Those wishing or needing to try an infusion pump will then easily move to continuous subcutaneous infusion and have the other method to fall back on when the pump malfunctions or they want a vacation from the device. When the decision is made to initiate continuous subcutaneous insulin infusion, the same conservatism as recommended for the transition to an additional conventional injection is indicated. The total daily dose should be reduced by about 10 percent and the pump set to deliver about half the total as a basal infusion. The remainder of the dose should be distributed roughly equally among the three main meals, but in a fashion taking both relative meal size and the relative resistance to insulin action at breakfast time into consideration.

With all complex insulin regimens, patients need extensive understanding of the physiology of their disorder

and its treatments. To achieve this, most diabetologists recommend consultation with a team experienced in the management of insulin-dependent diabetes mellitus and education of patients.

Objectives of Management

Decisions concerning the use of insulin naturally depend on specific objectives of treatment. Unfortunately, we still do not know exactly what sort of glycemic control is necessary to prevent or reduce the various complications of diabetes. We do not even know the relative contributions of an elevated mean plasma glucose level and the variability of glucose about that level. Some evidence suggests that restriction of maximal plasma glucose values to less than 200 mg per dl (180 mg per dl blood glucose) minimizes risk of microvascular complications.[91] Maintenance of much lower values seems necessary to minimize fetal risk during a diabetic woman's pregnancy, probably with a mean plasma glucose level below 120 mg per dl (105 mg per dl blood glucose).[92] The glycemic threshold for increased atherosclerotic risk is unknown, but may also be low.[93,94] Thus, our present view of what is desirable glycemic control must remain tentative. Achieving normal plasma glucose content is the ideal goal, with daily variation of plasma glucose values entirely within the 60 to 140 mg per dl range (55 to 125 mg per dl blood glucose) and without abrupt excursions. Present methods do not achieve this for most persons without endogenous insulin except with extreme effort over limited periods, such as during pregnancy. A more realistic goal for all diabetic persons taking insulin is to maintain the plasma glucose level within the 60 to 180 mg per dl range (55 to 160 mg per dl blood glucose). This degree of control can be achieved most of the time by adequately motivated patients who have a good understanding of the use of our tools for treatment. Concentrations of glucose in this range correspond to high-normal or minimally elevated glycosylated hemoglobin values. A leading difficulty in safely achieving these objectives is the lack of an adequate objective test for detecting hypoglycemic events,[64] coupled with the relative inability of many persons who have neuropathy[95] or who are taking sympathetic blocking drugs[96] to perceive hypoglycemia. Frequent or severe hypoglycemia should not be accepted as a necessary accompaniment of nearly normal glucose values.

Establishing physiologically desirable and theoretically attainable therapeutic objectives does not solve a clinician's problem. Patients have the larger say as to what objectives will actually be pursued. A true process of negotiation between a physician and patient must establish what clinical and glycemic outcomes both are willing to seek.[97] Modest and attainable objectives should be set at first. Renegotiation may set more ambitious goals when the initial objectives are achieved and sustained. Diabetic control is a lifelong task, and both physician and patient must consider what approach will work best in the long run.

The Future

The management of diabetes is in flux. We shall soon have more new tools including human insulin, better insulin delivery systems, perhaps systems with the ability to sense glycemic changes and perhaps simpler, cheaper and more accurate means of self-measurement of glucose content. The possible role of sulfonylureas in potentiating the effectiveness of injected insulin may soon be clarified, and very likely other hypoglycemic compounds that can be taken orally will come into use. Transplantation of intact pancreases or of β-cells and prevention of many cases of insulin-dependent diabetes mellitus by immunization against certain strains of viruses may become feasible and even routine. Even so, a systematic approach to the management of hyperglycemia will continue to be necessary, one that incorporates individual clinical judgments based on an understanding of the physiology of diabetes and the capabilities of our treatments.

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Specialty Conference

Protean Manifestations of Perinatal Enterovirus Infections

Discussants

STEPHEN A. SPECTOR, MD, *and* RICHARD C. STRAUBE, MD

From the Division of Infectious Diseases, Department of Pediatrics, University of California Medical Center, San Diego.

RICHARD C. STRAUBE, MD:* *The cases of five patients will be discussed, including a set of twins and their parents, in whom infections with echovirus type 4 occurred.*

Reports of Cases

CASE 1. The mother of the twins (see cases 2 and 3), a 24-year-old woman, was admitted to hospital at 36 weeks' gestation, six days before the infants' delivery. For eight hours she had had malaise, myalgias, headache, fever and a mild sore throat. Similar symptoms had developed in her sister about two weeks before.

On admission she was noted to be in active labor, which ceased after the administration of isoxsuprine hydrochloride. During the four days in hospital she continued to have intermittent fevers spiking to 39.5°C (103.1°F), with shaking chills. Cultures of blood, urine, vaginal, amniotic fluid and throat specimens were negative for bacteria. On the third day a diffuse macular erythematous rash developed over the abdomen and thighs, which faded during the next 18 hours. At that time mild diarrhea also developed. Fever subsided on the fourth hospital day and the patient was discharged the following day.

About 36 hours after discharge, she came to hospital after spontaneous rupture of the membranes and in active labor. Because the first twin was in breech presentation, cesarean section was done.

CASE 2. Twin A was a 2,280-gram male infant whose Apgar scores were 8 and 9 at one and five minutes. The infant was well until the second day of life when his body temperature became unstable and he began vomiting bile-stained material. A chest x-ray film showed infiltrates. Laboratory studies disclosed a leukocyte count of 4,400 per cu mm, with 52 percent polymorphonuclear leukocytes and 9 percent band forms, and a platelet count of 377,000 per cu mm. Lumbar puncture showed four leukocytes (100 percent mononuclear cells) and normal concentrations of protein and glucose. Bacterial cultures of blood, urine and cerebrospinal fluid specimens were sterile.

The patient was given ampicillin and gentamicin sulfate and did well until the fourth day of life, when a generalized erythematous macular rash developed on the trunk and extremities. The rash blanched with pressure and faded over the course of about 18 hours. Intermittent apnea and bradycardia developed and activity was noted to be decreased. On the fifth day of life the platelet count fell to 5,000 per cu mm and the serum aspartate aminotransferase (AST, formerly serum glutamic oxaloacetic transaminase [SGOT]) value was 240 IU. By the sixth day of life the patient was hypotensive and had poor peripheral perfusion and oliguria. Hepatomegaly was noted for the first time, and the AST level rose to 6,650 IU. Active bleeding developed and the hematocrit dropped from 40 percent to 19 percent. The platelet count was 10,000 per cu mm and his prothrombin time and partial thromboplastin time were both notably prolonged. The infant received the first of multiple double-volume exchange transfusions. On the seventh day of life, an enterovirus was isolated from specimens of nasopharynx and feces that was subsequently identified as ECHO 4 virus.

The patient received daily double-volume exchange

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transfusions for the treatment of continuing disseminated intravascular coagulation documented by tests positive for fibrin-split products, decreased platelet counts, low fibrinogen and thrombocytopenia. By the second week of life, the patient's AST and serum alanine aminotransferase (ALT, formerly serum glutamic pyruvic transaminase [SGPT]) levels fell to about 80 IU (normal values for both are 10 to 30 IU). By one month, the disseminated intravascular coagulation resolved. The exchange transfusions were continued, however, for control of hyperbilirubinemia. When the patient was seven weeks old, exchange transfusions were discontinued when the bilirubin level was 21 mg per dl. The bilirubin has been maintained in the range of 5 to 6 mg per dl as liver function has improved.

CASE 3. Twin B weighed 2,420 grams and Apgar scores were 8 and 9 at one and five minutes. Shortly after birth he was noted to have grunting and retractions. Chest roentgenogram revealed infiltrates. Laboratory studies showed a leukocyte count of 6,800 per cu mm with 38 percent polymorphonuclear leukocytes and 1 percent band forms. The cerebrospinal fluid contained 6 leukocytes per cu mm (100 percent mononuclear cells), the protein concentration was 152 mg per dl and the glucose value was normal.

The patient was given ampicillin and gentamicin and on the second day of life vomiting of bile-stained material developed, which resolved over the next 24 hours. Cultures of specimens of blood, cerebrospinal fluid and urine were negative for bacteria. Four days after birth an erythematous rash developed that was identical to that of his sibling. His rash also faded over the course of 18 to 24 hours. The following day for the first time he had hepatomegaly, lethargy, intermittent apnea and bradycardia. When he was six days old, clinically evident disseminated intravascular coagulation developed, with positive findings for fibrin-split products, decreased platelets, a falling hematocrit and prolonged prothrombin and partial thromboplastin times. He received a double-volume exchange transfusion but there was no improvement. The infant progressively worsened and died on the 13th day of life after a major pulmonary hemorrhage. Premortem cultures of specimens from nasopharynx and rectum, as well as postmortem cultures of liver, spleen, heart, brain, blood and intestines, all grew ECHO 4 virus.

CASE 4. On the second day of the twins' illness the father of the twins had diarrhea, fever and malaise. Two days later he had a rash. All of his symptoms including the rash resolved over the next two days. ECHO 4 virus was subsequently isolated from his nasopharynx.

CASE 5. An infant weighing 3,090 grams was born after a 36-week gestation. He was transferred to University Hospital shortly after birth because of grunting and retractions. A right-sided pneumonia was found and treatment was begun with ampicillin and gentamicin. Cultures were negative and the patient did well. He was in the bed next to the twins from the seventh to ninth days of his life. On the tenth day, the patient having been transferred back to the referring hospital, a temperature of 39.3°C (102.7°F), diarrhea, cough and nasal congestion developed. He was returned to University Hospital. A leukocyte count was 10,600 per cu mm with 43 percent polymorphonuclear leukocytes and 39 percent band forms. A lumbar puncture examination showed 250 leukocytes per cu mm (45 percent polymorphonuclear cells), a glucose level of 33 mg per dl (blood glucose, 86 mg per dl) and a protein level of 75 mg per dl. Ampicillin and gentamicin treatment was started. Repeated apnea required intubation. On the 11th day of life hepatomegaly was noted for the first time and there was poor peripheral perfusion. Viral cultures of a specimen of the cerebrospinal fluid grew ECHO 4 virus The patient was rapidly weaned from the ventilator over the next three days and was discharged at the age of 19 days, doing well.

In summary, we have presented the case of a woman in whom enteroviral disease developed six days before delivery. She was delivered of twins in whom overwhelming viral infections developed. One infant died, while the other improved after a very stormy course. In a baby exposed to these infants between seven and nine days of life meningitis developed that was caused by the same virus. The father of the twins had a relatively mild illness. Viral cultures of specimens from rectum and nasopharynx were done on all other infants in the nursery but no other baby was found to be infected.

Discussion

STEPHEN A. SPECTOR, MD:* These five cases represent the broad spectrum of clinical disease associated with enteroviral infections. Although we usually think of enteroviral infections of children as causing fever, rash, gastroenteritis or self-limited meningitis (or all of these), they may result in severe fulminant disease in the neonatal period. I shall review the diseases associated with enteroviruses in newborns, emphasizing recent published studies concerning fatal echovirus infections in young infants.

The enteroviruses, which include the polioviruses, echoviruses and coxsackieviruses, are members of the picornavirus group, which also includes the rhinoviruses. The enteroviruses are small, single-stranded RNA viruses. There were recently 67 distinct serotypes: polioviruses 1 to 3, echoviruses 1 to 34 (echovirus 10 has been reclassified reovirus 1, echovirus 28 has been reclassified rhinovirus type 1A and echovirus 34 is a strain of coxsackievirus A 24), group A coxsackieviruses 1 to 24 (coxsackievirus A 23 is identical to echovirus 9), group B coxsackieviruses 1 to 6 and enteroviruses 68 to 71. Classification of enteroviruses has in the past been confusing and frequently somewhat arbitrary. New strains of enteroviruses are now given a number (enterovirus 68, 69 and the like) and we are now at enterovirus 71.[1]

Enteroviruses can be propagated in a wide range of tissue cultures, including primary monkey kidney cells, human embryonic fibroblasts, human embryonic kidney

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(HEK), HeLa and human amnion cells. Most enteroviruses can be isolated using two of these culture systems. Some coxsackievirus A strains, however, can only be detected by inoculating newborn mice.

Frequently, viral diagnoses are not recorded either because culture specimens are improperly obtained or transport of specimens is inadequate for viral growth. Enteroviruses can most easily be grown from stool specimens or rectal swabs. Persons infected with an enterovirus may continue to have virus in their feces for several weeks following the acute infection. Isolation of enterovirus from the feces is suggestive, therefore, of an acute viral infection, but may indicate a recent past infection rather than being the cause of a patient's acute illness. Positive enteroviral cultures from cerebrospinal fluid are of course much more indicative of the cause of the illness. Cerebrospinal fluid can be an excellent source for the isolation of enteroviruses in patients with meningitis if specimens for culture are obtained at the right time during infection. The earlier in the acute illness that a cerebrospinal fluid specimen is obtained for viral culture, the greater is the chance of isolating the causative enterovirus. Frequently the lumbar puncture is done in the middle of the night when the viral diagnostic laboratory is closed or at a hospital where specimens must be transported to another facility for culture. In such cases, specimens should be kept at 4°C either in crushed ice or in a refrigerator, and transported on crushed ice to the laboratory. Enteroviruses are among the most hardy of viruses and will grow in cultures if transported properly. Freezing at −20°C will decrease the chance of recovering the virus and should be avoided. Because enteroviruses are frequently found in the cerebrospinal fluid of patients with meningitis for short periods, the initial cerebrospinal fluid specimen drawn for diagnosis is more likely to yield virus than a specimen obtained in 12 to 18 hours. It is also important to remember that though enteroviruses survive for extended periods in the gastrointestinal tract, they occasionally may be isolated from the pharynx, buffy coat or urine. In addition, although we frequently think of enteroviruses as causing infections in the summer and fall, as in the cases presented, the clinical disease occurs throughout the year. This is true in temperate climates as well as in southern California where warm weather occurs year round,[2] so that appropriate cultures are warranted in all patients who potentially have enteroviral disease.

Poliovirus is the prototypic enterovirus and has been studied in detail. During the time of poliovirus epidemics, neonatal poliomyelitis was uncommon, probably because most adults were immune from having had a previous natural infection. Pregnant women in whom primary poliovirus infections developed during the 1940s frequently had major complications.[3] Although the polioviruses as well as other enteroviruses have not been reported to cause congenital malformations, abortions and stillbirths were observed in 20 percent of mothers in whom primary poliovirus infections developed during their pregnancies. Severe neonatal disease was common in infants born to infected mothers. Bates[4] found that in 43 of 44 infants infected with poliovirus, paralysis developed and almost half of these infants died. Only 25 percent of the original 44 infants were normal after five years. Fortunately, because of the successful poliovirus vaccine program in the United States, neonatal poliomyelitis now rarely occurs.

Coxsackieviruses A and B and echoviruses appear not to be a cause of abortion or stillbirth. They may be associated, however, with an increased incidence of premature birth. The association of coxsackievirus B with congenital heart disease is controversial, but most studies have found no association between infection with coxsackievirus B and structural congenital heart disease.[5,6] Coxsackievirus type B is a well-known cause of severe myocarditis and 25 percent to 100 percent of infants infected die of their disease.[7,8] Infants who survive acute myocarditis due to coxsackievirus B usually have no cardiac residua on long-term followup.[9]

Newborns infected with echoviruses generally have nonspecific, mild disease. Lake and co-workers[10] studied 27 infants with echovirus and coxsackievirus infections. Most of the infants were infected either before four days of age, suggesting transplacental or puerperal infection, or after ten days old, suggesting postnatal exposure. Generally the clinical findings associated with neonatal enteroviral infections are nonspecific. They include fever, poor feeding, diarrhea, abdominal distention and irritability, all of which occur in over half of the infants with infections. An erythematous macular papular rash occurs in about 40 percent of infants with enteroviruses and is frequently the best clue to the presence of viral infection. A complete blood count and differential cell count are not helpful in my experience in distinguishing between enteroviral infections and bacterial disease.

To return to the cases presented by Dr Straube—about five to six days before the time that the mother gave birth, fever, cough, headache, diarrhea and rash developed. A week later similar symptoms developed in her husband. The erythematous macular papular rash present in both mother and father suggests an enterovirus as the causative agent. Twins A and B initially had similar findings with fever and rash. Their diseases progressed to disseminated intravascular coagulation and twin B died. A third infant in the special care nursery also became infected with echovirus type 4. Epidemiologic data suggest that this baby was nosocomially infected with an echovirus type 4 likely transmitted via nursery personnel from one of the twins.

The outcomes in the three babies were strikingly different, suggesting that dosage or timing of the babies' viral invasion or an immunologic defect was important in determining the severity of disease. Echovirus type 4 infections are usually associated with mild disease even in young infants. In 14 cases reported[11] in babies younger than 6 weeks of age who were infected with echovirus type 4, all had fever and irritability, and in about a third vomiting, cough, anorexia and rash de-

veloped. Only one of the 14 infants had diarrhea. There were no fatal infections.

A large outbreak of echovirus type 4 disease has recently occurred in Panama City.[12] From September 23 to October 29 of 1981, almost 750 instances of aseptic meningitis were identified in children and adults. The peak incidence of echovirus type 4 infections occurred in children 4 to 14 years old. A large number of infants younger than 1 year of age were also infected. No deaths were reported, however.

An outbreak of echovirus type 11 disease occurred in San Diego and the rest of the United States in 1979. We have recently reported two fatal cases of echovirus type 11 that occurred during that period.[13] One of the infants presented in a similar fashion to the twin infants described here. The mother had become febrile within 12 hours of delivery. The baby was born without complications, but at four days of age fever, respiratory distress, hepatitis, disseminated intravascular coagulation and seizures developed. The baby eventually died of fulminant echovirus type 11 disease. Modlin[14] and associates[15] observed four infants who died of overwhelming disease due to echovirus type 11. When infants who died of their infections were compared with newborns who became infected with echovirus but had mild illness, a consistent pattern evolved. Fatal disease in the neonatal period was associated with maternal infection within four to five days of delivery. Babies born following five days of maternal infection received transplacental maternal viral specific IgG antibody and their infections were mild or there were no symptoms. Infants born within five days did not receive maternal antibody and were at high risk of severe, fatal echovirus disease developing. Similar findings have been described for perinatal primary varicella zoster virus (chickenpox) infections, which suggests the important protective role of maternal antibody in these infections.

The second case of fatal echovirus type 11 infection was atypical. That infant was 3½ months old at the time of infection. His infection progressed from an upper respiratory tract infection with neck swelling to fulminant disease in which there were neutropenia, hepatitis, meningitis, pericarditis and disseminated intravascular coagulation. Neck swelling was the prominent presenting clinical finding in this baby and at postmortem examination, myositis of the strap muscles with destruction of skeletal muscles was seen, reminiscent of experimental studies done on mice infected with coxsackievirus type A. The myocarditis seen in this infant was indistinguishable from myocarditis caused by coxsackievirus type B. It is possible that this 3½-month-old infant had an unrecognized immunologic disorder that resulted in his fatal echovirus disease.

The pathologic findings in the twin infant who died consist of diffuse hemorrhagic necrosis of virtually all organ systems. In patients with fatal infantile echovirus disease, postmortem examinations have usually shown disseminated multiorgan necrosis with acute hemorrhage.[13,16-18] The devastating, extensive organ involvement in these infections is certainly in great contrast to the usual mild and self-limited enterovirus disease with which we are familiar.

The long-term prognosis in young children with enteroviral meningitis is unclear. Sells and colleagues[19] found that children who had central nervous system infections with enteroviruses during the first year of life had a significantly smaller head circumference than controls, significantly lower mean IQ scores and depressed development of language and speech. Other studies have detected no difference in any of these areas.[20,21]

Institution of adequate measures of infection control cannot be overemphasized in nursery settings when an infant has an enterovirus infection. A large number of nursery outbreaks have been described,[22] and premature infants are at increased risk of having serious disease when infected. Any infant with known or suspected enterovirus infection should be isolated. Nursing care schedules should be adjusted so that as few nurses as possible care for an infant so infected. Strict enteric precautions should be observed at all times and hospital personnel should wear gowns and gloves when handling an infant, dirty diapers or respiratory secretions. Good handwashing is, of course, crucial and should be conscientiously practiced.

Procedures for the prevention of enterovirus infections other than poliovirus are currently inadequate. Unlike poliovirus that causes severe infections frequently enough to warrant wide-scale immunization, other enterovirus infections usually do not result in debilitating disease. Furthermore, because there is such a large number of enteroviruses, a vaccine against all possible types is impractical. The use of a passive antibody in one person with a specific immunoglobulin deficiency has been reported to be successful.[23] It is unlikely that infants with severe disease will benefit from such an antibody once their disease has developed. Passive high titer antibody may be beneficial to infants born to mothers who have enteroviral infections within five to seven days of delivery, similar to the use of varicella zoster immune globulin in mothers who have chickenpox before delivery. There is currently no antiviral therapy effective against enteroviruses. Experience with patients such as those presented strongly suggests that antiviral therapy would be of benefit and should stimulate development of chemotherapeutic agents.

PHYSICIAN IN THE AUDIENCE: *Should delivery be delayed in a woman with enterovirus infection?*

DR SPECTOR: Certainly an elective cesarean section should not be done when a woman is suspected of having an active enterovirus infection within a few days of the scheduled delivery. When a woman is in active labor, the risk to mother and infant of delaying delivery must be weighed against the potential benefits. If amniotic membranes have ruptured, delay of delivery may increase the risk of amniotitis in the mother and serious bacterial infection in the infant.

PHYSICIAN IN THE AUDIENCE: *In the absence of avail-*

able high titer antibody against a specific enterovirus, should an infant be transfused with maternal plasma?

DR SPECTOR: That is an interesting possibility. To my knowledge no systematic studies have been done to explore this concept, but transfusing an infant with maternal blood containing antibody may be helpful in treating enterovirus infection. These transfusions should be done before the development of clinically significant disease in an infant. Once enteroviral disease has developed, I doubt if antibody therapy would be beneficial.

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Medical Practice Questions

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Bilio-pancreatic Bypass Surgery for Morbid Obesity

QUESTION:

Is bilio-pancreatic bypass surgery for morbid obesity considered accepted medical practice or is it considered investigational?

OPINION:

In the opinion of the Scientific Advisory Panel on General Surgery, bilio-pancreatic bypass surgery for morbid obesity should clearly be considered an investigational surgical procedure at this time. A larger number of patients and considerably longer, detailed follow-up are necessary before this technique can be properly evaluated and adopted as established practice. The history of surgical treatment of obesity would suggest that a follow-up period of more than two years is necessary to determine that an intestinal bypass operation is free of long-term complications and effective in accomplishing weight loss.

There has been insufficient published literature on this procedure to adequately document its safety and efficacy.

Medical Staff Conference

Renal Sodium Retention in Liver Disease

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR SLEISENGER:* *This Medical Staff Conference will be given by Dr Robert Alpern. Dr Alpern went to college at Northwestern University and then attended medical school at the University of Chicago. He received his training in internal medicine at Columbia University and in nephrology here at the University of California, San Francisco, Medical Center. This year he joined the faculty as an assistant professor in the Department of Medicine. He will discuss the mechanisms of sodium retention in liver disease.*

DR ALPERN:† Renal sodium excretion is normally regulated so that extracellular fluid volume is maintained within normal limits. Any maneuver that increases extracellular fluid volume will lead to a prompt and sustained natriuresis until the volume returns to normal. In patients with cirrhosis, this homeostatic mechanism malfunctions and large increases in extracellular fluid volume are accompanied by continued renal salt retention and ascites formation. The purpose of this review is to synthesize the available data into an understanding of the mechanisms of renal salt retention. Implications for treatment will also be discussed.

In patients with cirrhosis, the kidneys are normal but respond to an inappropriate "signal" by retaining salt. The primary step in the generation of this signal and thus ascites formation is hepatic venous outflow obstruction (postsinusoidal). Thus conditions such as cirrhosis and Budd-Chiari syndrome, which are associated with functional hepatic venous outflow obstruction and elevated sinusoidal pressures, lead to ascites. Conditions associated with presinusoidal vascular obstruction such as portal vein thrombosis and schistosomiasis cause portal hypertension but sinusoidal pressures are normal. These conditions do not lead to ascites formation until late in the disease when hepatic architecture is destroyed.

Normally, pressures in the hepatic sinusoids cause fluid to move from the sinusoids across the endothelial cells and into the space of Disse. This space is connected with the hepatic interstitium and the fluid is carried by lymphatic vessels through the thoracic duct and returned to the plasma. As sinusoidal pressures increase, fluid moves into the space of Disse at a faster rate. Due to a fixed size of the ostium of the thoracic duct, the rate at which interstitial fluid can be returned to the vascular space is limited. When sinusoidal pressures increase to such a degree that fluid leaves the sinusoid at a faster rate than the thoracic duct can return it, interstitial fluid weeps off the liver into the peritoneal space and forms ascites.[1] In addition, some ascites will form from fluid weeping from the interstitium of the bowel due to portal hypertension. This contribution is however not as great since, as stated above, portal hypertension alone does not lead to ascites formation.

In normal livers and early in cirrhosis, the endothelium that separates the sinusoid from the space of Disse is very leaky to proteins. Thus, protein concentrations are similar in the sinusoid and in the space of Disse, and plasma oncotic pressure is not an important determinant of the rate of ascites formation.[1] Later, a process referred to as "capillarization" occurs and this endothelium becomes less permeable to protein.[1] At this time, plasma oncotic pressure becomes a more important determinant of ascites formation.

Exactly how the hepatic venous outflow obstruction leads to sufficiently high sinusoidal pressures for ascites to form is controversial. The "classical" theory predicts that the degree of hepatic venous outflow obstruction is sufficient in the presence of normal splanchnic perfusion to cause ascites. According to this theory, hepatic venous outflow obstruction leads to increased sinusoidal and portal pressures, whereas liver disease leads to hypoalbuminemia (Figure 1). These abnormalities then

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cause the formation of ascites in the presence of normal splanchnic perfusion. Because the ascitic fluid is formed by removing fluid from the intravascular space, intravascular volume will decrease. This will lead to low venous filling pressures and a low cardiac output that will be sensed by baroreceptors and cause renal salt retention. Renal salt retention will lessen the degree of intravascular volume depletion, maintain splanchnic perfusion and thus maintain the high sinusoidal pressures that cause ascites. According to this formulation, the development of ascites is the primary event that leads to intravascular volume depletion and renal salt retention.

There are, however, a number of predictions from this theory that have not been confirmed when measured. The most important of these are hemodynamic. The classical theory predicts that extrasplanchnic plasma volume is decreased and that cardiac output is low. When measured, these values have varied among patients, but have rarely been low.[2-5] Plasma volumes have in fact been higher than normal in patients with cirrhosis.[2,3] This may be due to increased splanchnic plasma volume rather than nonsplanchnic plasma volume and is therefore difficult to interpret in humans. Cardiac outputs tend to vary from normal to very high but are rarely decreased.[2,4,5] The cause of this high cardiac output will be discussed below. These hemodynamic findings are clearly not compatible with the classical theory of ascites formation.

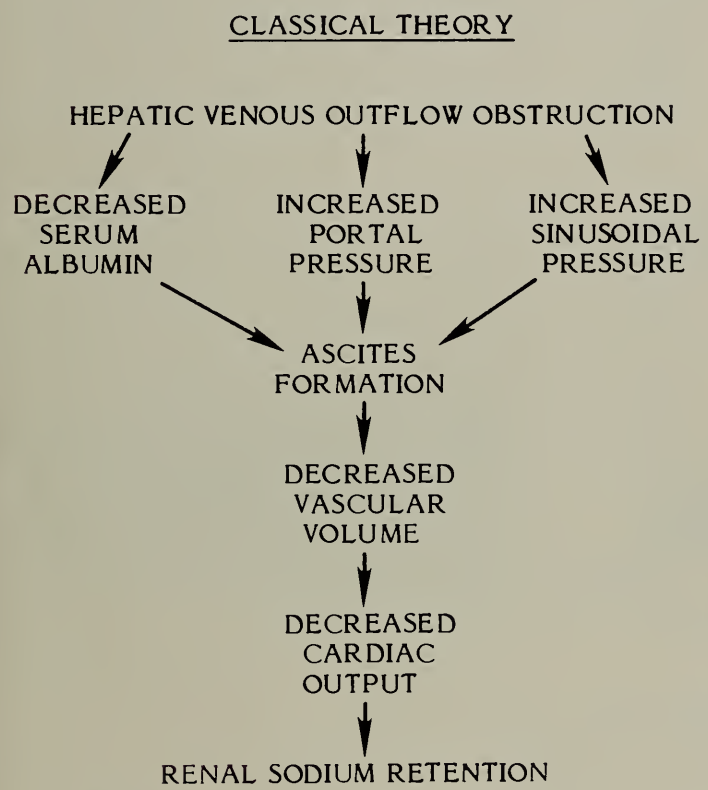

Figure 1.—Classical theory of ascites formation.

These observations have led Lieberman and colleagues[6] to propose the overflow hypothesis (Figure 2). Hepatic venous outflow obstruction is once again viewed as the primary event that leads to increased sinusoidal and portal pressures and hypoalbuminemia. However, hepatic venous outflow obstruction in the presence of normal splanchnic perfusion does not lead to sufficiently high sinusoidal pressures to cause ascites. Hepatic venous outflow obstruction does cause primary renal salt retention, which expands the plasma volume. This leads to the observed increased cardiac output and further raises sinusoidal and portal pressures, leading to movement of fluid into the interstitial space and ascites formation.

The best evidence in favor of the overflow hypothesis has come from studies done in dogs using a model of cirrhosis.[7-9] In this model, in dogs fed dimethylnitrosamine, liver disease that is histologically indistinguishable from Laennec's cirrhosis develops in six to eight weeks. On day 16 after development of progressive liver disease (Figure 3), sodium excretion falls below sodium intake and there is net sodium retention.[7] According to the classical theory, sodium retention should not start until after ascites forms. In these studies, however, ascites did not form until day 26. The absence of ascites was proved by physical examination, paracentesis through the most dependent portion of the abdomen

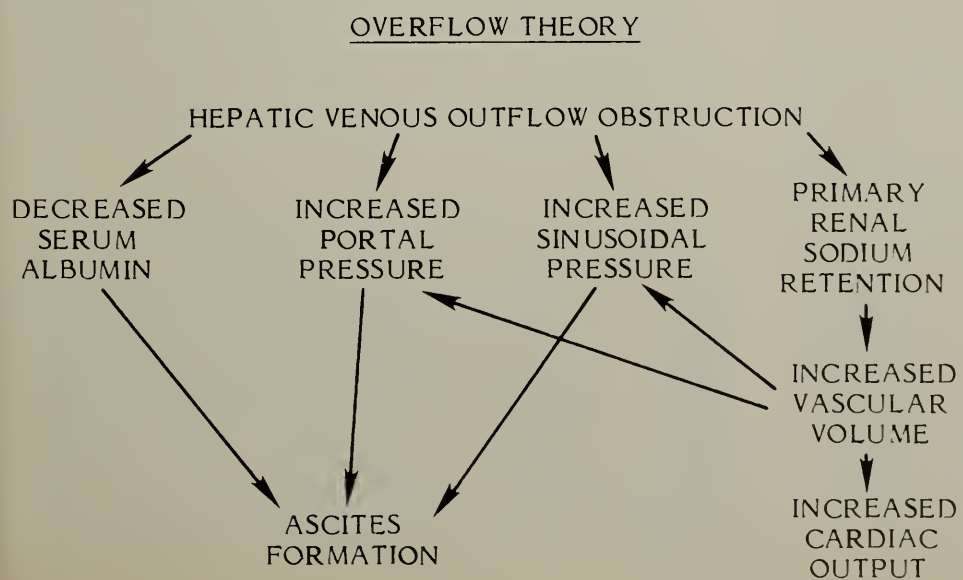

Figure 2.—Overflow theory of ascites formation.

and in some dogs by laparotomy. Sodium retention preceding ascites formation has also been found in rats with experimental cirrhosis.[10] As can also be seen in Figure 3, plasma volume increases in the period of sodium retention and increases further when ascites forms. These results are consistent with measurements in humans and once again could be explained by increased splanchnic plasma volume rather than extrasplanchnic volume. In additional studies, however, the superior and inferior mesenteric arteries, the celiac axis and the portal vein were ligated before measuring the plasma volume.[7] This prevented communication with the splanchnic vasculature and allowed the measurement of extrasplanchnic plasma volume, which was elevated. To further prove that extrasplanchnic plasma volume was increased, these authors repeated the above studies in dogs with end-to-side portacaval shunts placed before inducing cirrhosis. This maneuver prevented increased splanchnic plasma volume but, once again, salt retention preceded ascites formation and was accompanied by increased plasma volume.[8]

Figure 4 shows the hemodynamics measured during these studies.[9] As can be seen, all hemodynamic parameters remained stable in the control, precirrhotic and postcirrhotic sodium balance periods (first three periods). Once sodium retention started, however, plasma volume

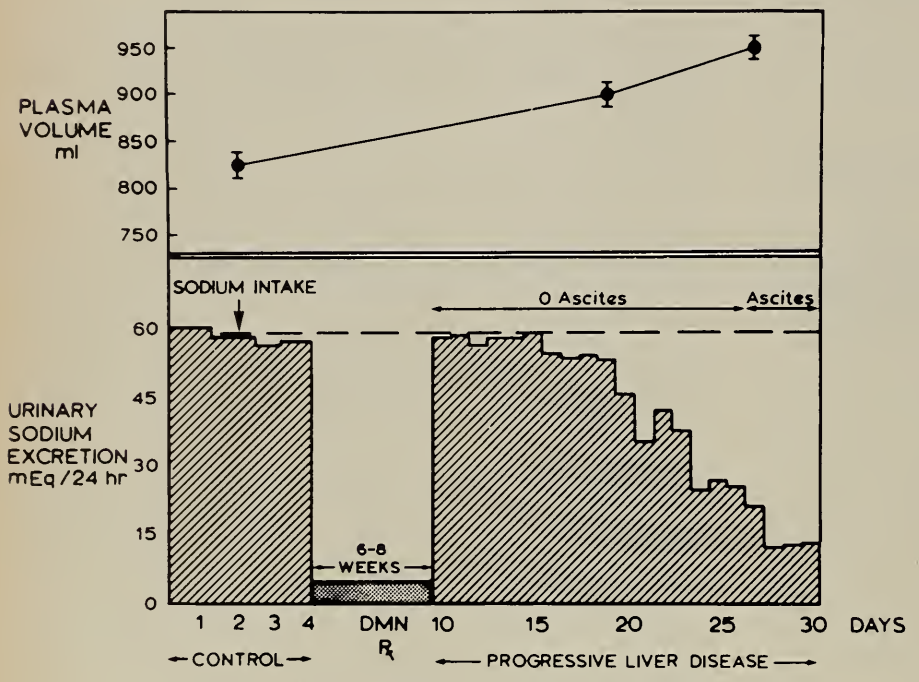

Figure 3.—Sodium balance and plasma volume are expressed as a function of time. Dashed line represents sodium intake and shaded areas represent sodium excretion. DMN = dimethylnitrosamine. Days on right side of figure are days after induction of cirrhosis. (Reprinted with permission from Levy.[7])

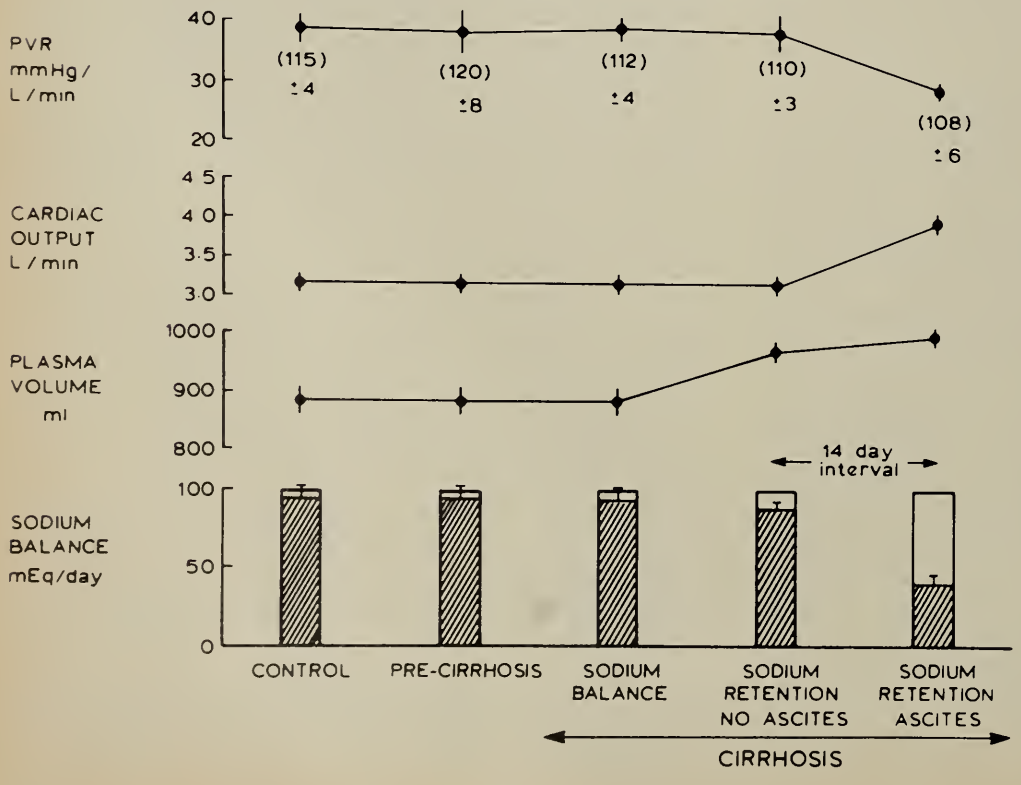

Figure 4.—Peripheral vascular resistance (PVR), cardiac output, plasma volume and sodium balance are listed for each of five periods of study. In the sodium balance graphs, the bars represent sodium intake and the shaded areas sodium excretion. Numbers in parentheses are mean blood pressure. (Reprinted with permission from Levy & Allotey.[9])

began to rise. At this stage, cardiac output and peripheral vascular resistance remained normal. When ascites occurred, plasma volume increased further, cardiac output increased and peripheral vascular resistance decreased. These studies thus show that renal sodium retention occurs in the absence of any hemodynamic factors known to lead to salt retention. These findings are exactly those predicted by the overflow theory.

One of the major problems with such an analysis is that the mechanisms that sense arterial volume may be more sensitive than the methods used to measure it. During the periods of cirrhosis, blood pressure was lower than in the precirrhotic periods (numbers in parenthesis, Figure 4).[9] Although the blood pressure difference may not have been statistically significant,[9] it may still have been enough to lead to the observed degree of salt retention. Indeed, in one series of dogs studied while anesthetized, blood pressure was significantly lower during cirrhosis than in the precirrhotic period.[7] Later I will discuss how a fall in blood pressure due to a lowered peripheral vascular resistance can lead to salt retention.

The distinction between the classical and overflow theories in human cirrhosis rests on the measurement of the effective arterial volume. This volume is sensed by the baroreceptors and leads to renal salt retention or excretion. It is a balance between cardiac output and peripheral vascular resistance. Lowering of cardiac output or peripheral resistance leads to a decreased effective arterial volume and hence renal sodium retention. The standard theory predicts that effective arterial volume is lowered in patients with ascites and is the cause of the renal salt retention. The overflow theory predicts that effective arterial volume is raised due to primary renal salt retention. Unfortunately, there is no easy way to measure the effective arterial volume, which explains why this controversy has persisted.

There are, however, a number of measurements that correlate with the effective arterial volume. Measuring these values may thus allow an educated guess as to the magnitude of the effective arterial volume. There are a number of hormones whose levels are regulated by the effective arterial volume and can thus be considered a measure of it. These include renin, aldosterone, antidiuretic hormone, and norepinephrine. In addition, the magnitude of the blood pressure can sometimes be useful in estimating the effective arterial volume.

The renin-aldosterone system has clearly been the best studied of these systems. Normally, decreased effective arterial volume stimulates renin release via changes in catecholamines and renal perfusion pressure. Renin released from the kidney cleaves angiotensinogen (renin substrate) to form angiotensin I, which is cleaved to form angiotensin II in peripheral vessels. Angiotensin II then stimulates the adrenal cortex to secrete aldosterone.

When measured in patients with cirrhosis, renin and aldosterone levels have varied from low to high. In considering these levels it is important to separate patients who do not have ascites (often referred to as compensated) from those who do (often referred to as decompensated). Patients without ascites have low to normal renin and aldosterone levels, but are in sodium balance and do not have abnormalities in renal sodium handling.[11,12] When one examines patients with ascites, mean renin and aldosterone levels are elevated, but individual values are often still normal.[11-14] This observation is difficult to reconcile with the classical theory, as all patients who have ascites and are retaining sodium should have a decreased effective arterial volume and high aldosterone levels. However, not all patients with ascites are retaining sodium. In fact, whereas in some patients with ascites sodium is actively retained and ascites accumulates, many are in balance and excrete a quantity of salt equal to their intake, and others have spontaneous diuresis. Thus, in examining the mechanism of sodium retention in cirrhosis with ascites, it is more appropriate to consider the renin and aldosterone levels with respect to the rate of sodium excretion.

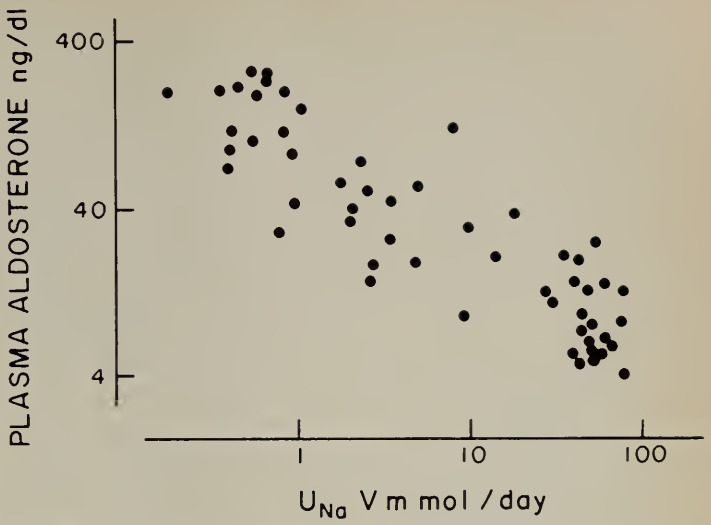

Figure 5.—Plasma aldosterone is plotted as a function of the rate of sodium excretion. $U_{Na}V$ = urine sodium excretion in millimoles per day. Both X and Y scales are logarithmic. (Reprinted with permission from Arroyo et al.[14])

When examined in this fashion, the plasma aldosterone concentration is found to correlate inversely with sodium excretion rate.[11-15] Figure 5 shows the results from one study.[14] All of the patients in this study had cirrhosis with ascites, but many excreted 50 to 100 mEq of sodium a day. As would be predicted by the classical theory, these patients have a normal effective arterial volume and thus a normal plasma aldosterone concentration. (Normal values for the assay used in this study are 10.5 ± 3.1 ng per dl.) Patients with lower rates of sodium excretion would be expected to have a low effective arterial volume and thus increased plasma aldosterone concentrations. This is exactly what has been found (Figure 5).[11-15]

Increased plasma aldosterone concentration can be due to an increased rate of aldosterone secretion or to a decreased rate of aldosterone metabolism. Aldosterone metabolism is impaired in liver disease (Figure 6).[16] This, however, is not responsible for the elevated

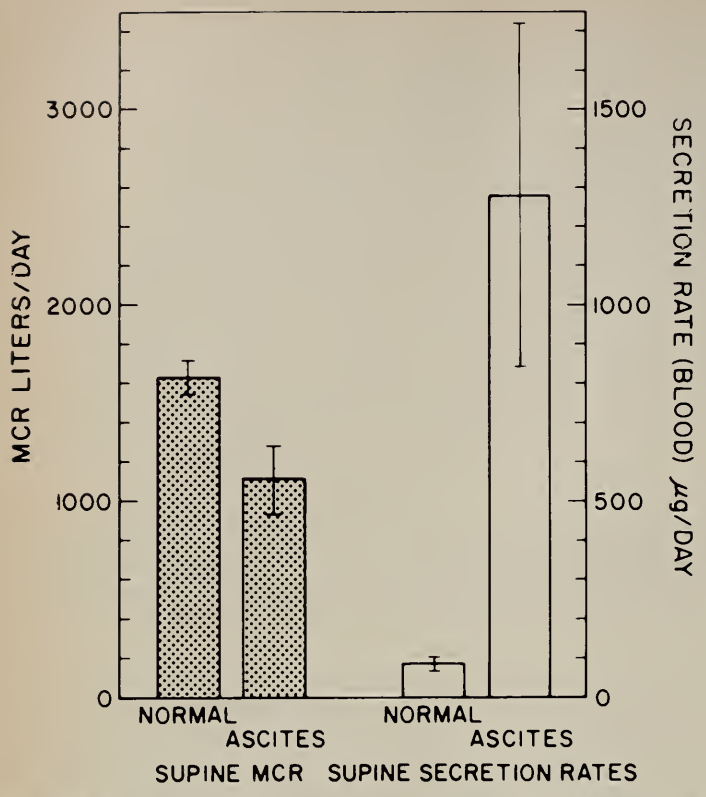

Figure 6.—Metabolic clearance rate (MCR) of aldosterone and aldosterone secretion rate are shown in normal persons and in patients with ascites. (Reprinted with permission from Rosoff et al.[16])

plasma levels of aldosterone in patients with cirrhosis. Aldosterone secretion rates are greatly elevated and are the major cause of the elevated aldosterone levels (Figure 6). Plasma aldosterone levels correlate well with plasma renin activities, which correlate well with the rate of renin secretion.[14] Thus, an increased rate of renin secretion leads to high renin levels, high angiotensin levels and high aldosterone secretion rates and levels. The renin level correlates poorly with renal plasma flow,[14,15] but correlates well with wedged hepatic vein pressure (a measure of sinusoidal pressure).[15] Earlier I stated that sodium retention and ascites formation correlated best with the presence of hepatic venous outflow obstruction and elevated sinusoidal pressure. It is therefore interesting that plasma renin levels correlate with wedged hepatic vein pressure.

While the above-described renin-aldosterone data are consistent with the classical theory, the overflow theory can also be modified to include them. According to this modification, raised sinusoidal pressures would lead directly to raised rates of renin secretion, which would then mediate the primary renal salt retention. Such an explanation could explain correlations between wedged hepatic vein pressure, renin levels, aldosterone levels and sodium excretion. However, one would not then expect elevated catecholamine and antidiuretic hormone levels in patients with cirrhosis who are retaining sodium.

Recent studies have examined the levels of norepinephrine in patients with cirrhosis. Similar to aldosterone levels, these values have varied from normal to elevated.[17] When examined as a function of the rate of sodium excretion, norepinephrine levels varied inversely with urinary sodium excretion rate.[17] Thus, similar to aldosterone levels, norepinephrine levels were raised in patients who were retaining sodium. In addition, plasma norepinephrine levels correlated with plasma antidiuretic hormone, renin and aldosterone levels.[17] These results are exactly as predicted for a decreased effective arterial volume. It seems unlikely that increased sinusoidal pressures would directly stimulate all three of these hormonal systems (that is, renin-aldosterone, antidiuretic hormone and norepinephrine).

Studies further examining this problem have used the technique of head-out water immersion. With this technique patients are immersed in a water bath up to their neck. This causes a large amount of fluid to move from the interstitial space into the vasculature and is equivalent to a large intravenous infusion of plasma ultrafiltrate. Such a maneuver raises effective arterial volume and sinusoidal pressure. The standard theory would predict that the rise in effective arterial volume would lower renin, aldosterone, antidiuretic hormone and norepinephrine concentrations. The overflow theory would predict that if raised sinusoidal pressures directly stimulated all of these hormonal systems, further increases in sinusoidal pressure induced by immersion would further raise hormonal levels. Epstein and coworkers found that although immersion does not uniformly lead to a natriuresis in all patients with cirrhosis and ascites, it does suppress renin and aldosterone levels in all patients.[18,19] Bichet and colleagues found a similar suppression of renin and aldosterone and in addition found that norepinephrine and antidiuretic hormone levels were suppressed by water immersion.[20] Once again, these results are most consistent with the classical theory.

Blood pressure can be considered a function of arterial blood volume and the degree of vasoconstriction. Patients with cirrhosis and ascites tend to have blood pressures on the low side of normal. In addition, they have a greater than normal fall in blood pressure when saralasin acetate is infused.[21] Saralasin is a competitive inhibitor of angiotensin II. Large drops in blood pressure during saralasin infusion imply that maintenance of blood pressure depends on angiotensin II. Low-normal blood pressure that is dependent on angiotensin II does not correlate with an increased effective arterial volume but with the decreased effective arterial volume predicted by the classical theory.

In summary, renin, aldosterone, antidiuretic hormone and norepinephrine levels are variable in patients who have cirrhosis with ascites. They however correlate inversely with sodium excretion and therefore are raised in patients who retain sodium. In addition, renin levels correlate with the wedged hepatic vein pressure and thus sinusoidal pressure. Low baseline blood pressures and large drops in blood pressure in response to angiotensin blockade further support the concept of a decreased effective arterial volume. In addition, water immersion, which raises effective arterial volume and

sinusoidal pressure, lowers renin, aldosterone, antidiuretic hormone and catecholamine levels. All of these findings are most consistent with a decreased effective arterial volume and the classical theory. As mentioned earlier, however, an increased cardiac output frequently found in patients with cirrhosis[2,4,5] is not consistent with the classical theory. This problem can be rectified by a slight modification of the theory.

The high cardiac output in patients with cirrhosis is associated with low mean arterial pressures and low peripheral vascular resistance.[2,4] The low peripheral resistance appears to be related to the presence of functional arteriovenous fistulae and selective vasodilation which have been found in the splanchnic, pulmonary, cutaneous and muscular circulation of patients with cirrhosis.[2,22-25] Dal Palù and colleagues injected serum albumin macroaggregates labeled with ^{131}I in order to identify arteriovenous fistulae. In the absence of fistulae, these aggregates are trapped in capillaries and never return to the general circulation. In patients with cirrhosis, these macroaggregates are able to bypass the capillaries and reappear in the general circulation.[22] Using this technique, Dal Palù and associates have found arteriovenous fistulae in the pulmonary, mesenteric and upper and lower extremity circulations.[22] Kontos and co-workers measured increased blood flow to the muscles and skin of the upper extremity.[23] This increased blood flow could not be attributed to increased oxygen consumption, anemia or thiamine deficiency. Postmortem injection studies of the splenic vasculature have also shown an intense proliferation of small arteries in patients with cirrhosis, although no arteriovenous fistulae were found.[25]

In normal persons, when an arteriovenous fistula is opened, peripheral vascular resistance decreases, cardiac output increases and diastolic and mean blood pressure go down. This leads to renal sodium retention, presumably because the increase in cardiac output is not enough to balance the increased vascular capacity (lowered peripheral resistance), and effective arterial volume is decreased.[26] Sodium retention then raises the venous filling pressure, further increasing the cardiac output until it matches the lowered peripheral resistance. At this point, effective arterial volume is normal, sodium excretion equals sodium intake and the patient is in balance.

Patients with cirrhosis, ascites and sodium retention are similar to normal persons with arteriovenous fistulae in that low peripheral vascular resistance leads to decreased effective arterial volume and renal sodium retention. They however differ in that they are unable to come into balance. Retained sodium does not remain in the vascular space and lead to increased venous filling pressures and cardiac output. Rather, retained sodium enters the abdomen as ascites, effective arterial volume remains decreased and renal sodium retention continues.

It thus appears that the experimental data can best be explained by a "modified classical" theory (Figure 7). According to this theory, hepatic venous outflow obstruction leads to increased sinusoidal and portal pressures and hypoalbuminemia that lead to ascites formation and a decreased effective arterial volume. This is similar to the classical theory. In this theory, however, hepatic venous outflow obstruction in addition leads to the formation of arteriovenous fistulae and peripheral vasodilation, which lead to an increased cardiac output and a decreased effective arterial volume.

The modified classical theory explains the coexistence of high cardiac outputs and low effective arterial volumes in patients with cirrhosis. In addition, it may provide an explanation for the studies using animals

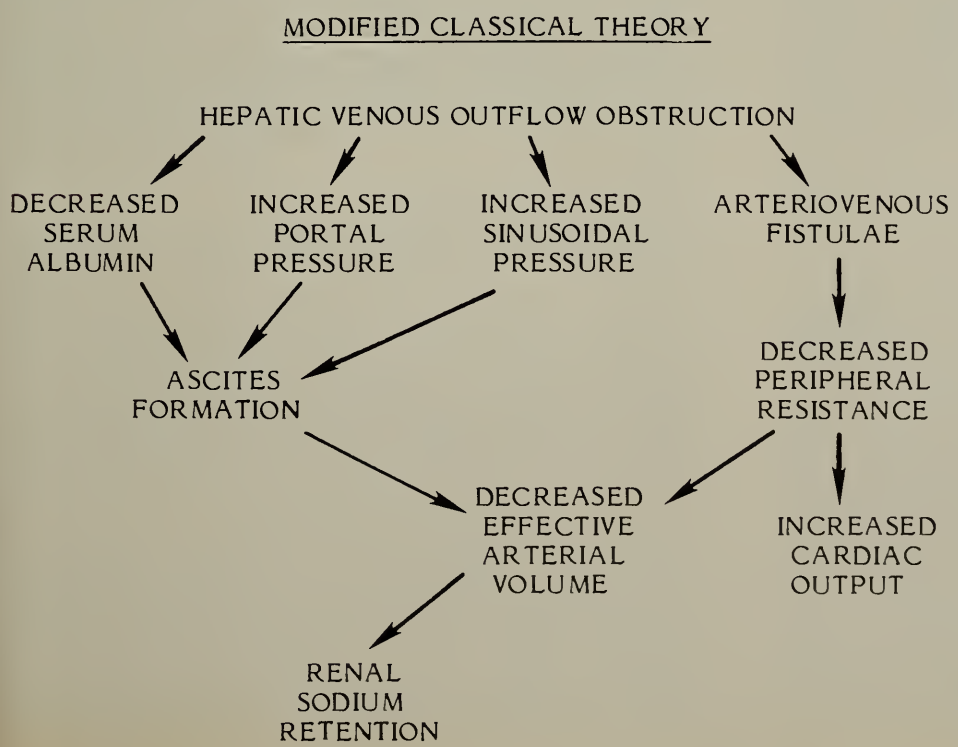

Figure 7.—Modified classical theory of ascites formation.

described earlier (Figures 3 and 4).[7-10] Sodium retention that precedes ascites formation could be due to arteriovenous fistulae formation leading to a lowered peripheral vascular resistance and a lowered effective arterial volume. It would be very difficult to measure this decrease in effective arterial volume initially. As discussed earlier, there was a tendency for the blood pressure to fall as cirrhosis developed in the dogs,[9] though this was not significant.

Hence, the experimental data are most suggestive of renal sodium retention occurring due to a decreased effective arterial volume. The tubular site of salt retention has been investigated using dilution studies and diuretic sensitivity. The major controversies concern the importance of increased salt absorption in the proximal and collecting tubules. Lowered effective arterial volume decreases renal blood flow and increases filtration fraction (glomerular filtration rate divided by renal blood flow), which should lead to a higher rate of proximal tubular sodium absorption. However, hypoalbuminemia can lower proximal sodium absorption.

Patients with cirrhosis and ascites are unable to excrete a free water load and are often hyponatremic. Infusion of mannitol or saline reduces this defect.[27,28] These results have been interpreted to imply that patients with ascites have increased proximal tubular salt absorption, which leads to decreased distal delivery. The decreased distal delivery is felt to be responsible for the diluting defect and to be corrected by mannitol or saline infusion. However, an alternative explanation of the results is that the diluting defect is due to raised antidiuretic hormone levels due to the lowered effective arterial volume, and that mannitol or saline infusion suppresses these levels.

Earley and Martino examined the magnitude of renal sodium absorption that remained after ethacrynic acid and chlorothiazide therapy.[29] This diuretic-resistant sodium absorption was greater in patients with cirrhosis than in normal controls, and the difference was attributed to a stimulation of proximal salt absorption. However, recent studies raise the possibility that this increased salt absorption may occur in the cortical collecting tubule (see below).

Perez-Ayuso and co-workers compared furosemide (160 mg a day) to spironolactone (300 mg a day) in a prospective, double-blind study on patients with cirrhosis and ascites.[30] Whereas only 11 of 21 patients had a diuresis in response to furosemide, 18 of 19 patients had a diuresis in response to spironolactone. In addition, 9 of the 10 patients who failed to respond to furosemide responded to spironolactone. All of the patients treated with furosemide had an increase in the rate of potassium excretion, including the patients who did not respond with natriuresis. Therefore, in all of the patients treated with furosemide, sodium absorption in the loop of Henle was inhibited and delivery to the collecting tubule was increased. But only in half of the patients did the excess delivered sodium reach the urine. These results, along with the effectiveness of spironolactone, suggest a greatly increased rate of salt absorption in the aldosterone-sensitive segment, the cortical collecting tubule. Indeed, this segment may have been the location of the ethacrynic acid-chlorothiazide independent sodium absorption observed by Earley and Martino.[29]

Epstein and associates observed that head-out water immersion suppressed aldosterone levels in all patients, but that some of these patients failed to have a natriuresis.[19] These authors concluded that aldosterone was not important in renal sodium retention in these patients. However, it must be remembered that the effect of changes in aldosterone concentration on tubular sodium absorption requires hours and thus may not appear during a short immersion study.[31]

Perez-Ayuso and colleagues also examined factors that correlated with responsiveness to low-dose spironolactone or any dose of furosemide. Patients who were diuretic resistant had higher renin and aldosterone levels and lower rates of sodium excretion before treatment.[30] There was no correlation with liver function. These results suggest that diuretic-resistant patients have the lowest effective arterial volume. Epstein and co-workers found similarly that the patients with the highest renin and aldosterone levels (and thus the lowest effective arterial volume) did not respond to water immersion with diuresis.[19]

In summary, patients with cirrhosis, ascites and renal salt retention have a decreased effective arterial volume, which is due to ascites formation and arteriovenous fistulae. These patients should therefore always be diuresed or paracentesed with caution. Patients who are resistant to diuretics have the lowest effective arterial volumes and should thus be treated most carefully. Although the exact locations of sodium absorption in the kidney require further investigation, it is clear that the cortical collecting tubule (aldosterone-sensitive segment) is of major importance. The proximal tubule is most likely also important, but this question requires further investigation. Spironolactone is the drug of choice for diuresis in these patients because of its potency and because it does not cause hypokalemia, a diuretic side effect that predisposes to hepatic encephalopathy.

Questions and Answers

PHYSICIAN IN THE AUDIENCE: *The normal response of a patient to an arteriovenous fistula requires renal salt retention, which increases the cardiac output. The limit to which a person can respond to progressively increasing fistulae is determined by the intrinsic myocardial function. Another factor that may be involved in these patients is that there may be some degree of underlying alcoholic heart disease that impairs the response to progressive fistulae formation.*

DR ALPERN: Patients who have cirrhosis have classically been felt not to have heart disease because of their high cardiac output. This is wrong. There was an interesting study done by Limas and colleagues in which they infused angiotensin II into patients with cirrhosis to raise the peripheral vascular resistance to

that of normal persons.[32] When this was done, filling pressures rose above normal and the authors concluded that many of these patients do have cardiac dysfunction.

PHYSICIAN IN THE AUDIENCE: *The modified classical theory would require then that fistulae be developing before some of the florid manifestations of salt retention. Is there any evidence to show that this is the case, histologically or functionally?*

DR ALPERN: Levy found that cardiac output was increased and peripheral vascular resistance decreased by 25 days after the induction of cirrhosis when dogs treated with dimethylnitrosamine had ascites.[9] The question is whether there was already an effect starting ten days earlier. I do not know of any data, but I would assume that it is possible.

PHYSICIAN IN THE AUDIENCE: *Those classic experiments of Epstein and co-workers that you showed involved large arteriovenous fistulae. It seems to me that to support your theory, which I think is very interesting, there would have to be a massive effect involving the systemic circulation. You should be able to show an increased mixed venous oxygen content. What evidence is there for this?*

DR ALPERN: About 20 years ago, Murray and coworkers actually did measure the arteriovenous oxygen difference and found that it was decreased.[2] The hemodynamic effect of these arteriovenous fistulae must be very large, as we are dealing with cardiac outputs of 10 liters a minute, which are insufficient to maintain an effective arterial volume. Fistulae have been identified in skin, muscle, the mesenteric circulation and in the spleen. I should add that this effect of fistulae has also been attributed by some people to just general vasodilation, which would have a similar hemodynamic effect.

PHYSICIAN IN THE AUDIENCE: *There is also compelling evidence for arteriovenous fistulae in patients with acute hepatic failure without preexisting liver disease. These patients have pulmonary right to left shunting that is completely reversible.*

DR ALPERN: It has been clearly shown that patients with cirrhosis tend to be hypoxic due to shunting in the lung.

PHYSICIAN IN THE AUDIENCE: *High cardiac output and low peripheral vascular resistance, though, can be accounted for by high levels of prostaglandin which have been present in these patients. Tachyphylaxis to angiotensin II has been demonstrated, due to prostaglandins.*

DR ALPERN: I think there could be any number of mechanisms. The modified classical theory would work with either general vasodilation or with arteriovenous fistulae. I think the findings with macroaggregated albumin are more suggestive of the presence of fistulae, but there certainly could also be a contribution from a general vasodilation, possibly prostaglandin mediated.

PHYSICIAN IN THE AUDIENCE: *According to your explanation of why ascites develops, there is actually less permeability of albumin in the liver. I am wondering why it is generally thought that giving albumin to increase the effective intravascular volume is ineffective because it ends up in the ascitic fluid.*

DR ALPERN: Initially the sinusoids are very permeable to albumin so that in early ascites formation the plasma oncotic pressure will not be a determinant of the rate of interstitial fluid formation in the liver, though it still would be a determinant in the splanchnic circulation. As the disease progresses, capillarization occurs, the sinusoids become impermeable to protein and protein oncotic pressures become very important. We usually see patients in that later stage because the fluid obtained on paracentesis is a transudate, which would imply that the protein is not getting into the ascitic fluid. Intravenous administration of albumin increases plasma oncotic pressure, which slows ascites formation, but it also increases sinusoidal pressures, which accelerates ascites formation. The net effect is that the rate of ascites formation usually increases. It is not clear how much of the albumin actually enters the ascitic fluid.

PHYSICIAN IN THE AUDIENCE: *We are classically taught that hepatorenal syndrome develops in patients while they are in hospital. Current studies at the Veterans Administration suggest that these patients have abnormal renal function when they are admitted. Are these findings compatible with your theory?*

DR ALPERN: I think that when patients are admitted to hospital with ascites they will classically have a decreased effective arterial volume. The measurement of glomerular filtration rate by creatinine clearance determination is inaccurate in these patients because they have low muscle mass and have very low creatinine generation rates. Inulin measurements would be more accurate. I think many of these patients will have low glomerular filtration rates when they are first admitted. We make a mistake with patients who are unresponsive to diuretics when we push harder with diuretic administration. We should not be pushing diuretics in these patients because they are the ones in whom hepatorenal syndrome is most likely to develop.

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Epitomes

Important Advances in Clinical Medicine

Dermatology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in dermatology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers or scholars to stay abreast of these items of progress in dermatology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Dermatology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, 731 Market St, San Francisco, CA 94103

Sunscreens

THE SUNBURN effects of ultraviolet light on epidermal DNA are well documented, and whereas a definite cause and effect relation between such damage and skin carcinogenesis is not certain, DNA damage induced by ultraviolet-B is thought to be an important component. An ideal sunscreen should protect against all biologic effects of ultraviolet radiation and not simply inhibit ultraviolet-induced skin erythema.

There have been recent attempts to evaluate sunscreens using different assay procedures. The standard human assay procedure is called the human sun protection factor (SPF) assay. Using volunteers, the minimal erythemal dose is determined in their skin where not previously exposed to sun by administering a series of dose increments of ultraviolet radiation using usually a solar-simulator light source. The next day, areas of skin are treated with the sunscreen to be tested and the ultraviolet radiation again delivered. The sun protection factor is calculated as the ratio of the minimal erythemal dose in protected skin to the minimal erythemal dose in unprotected skin.

Many commercially available sunscreens have sun protection factor readings of 15; this means that a person can stay in the sun for 15 times the length of time that would produce skin erythema without the sunscreen.

Sunscreens containing para-aminobenzoic acid (PABA) and its esters have been shown to protect against ultraviolet-induced changes in epidermal DNA synthesis rates in hairless mice. They have also been shown in hairless mice to protect against photocarcinogenesis.

Whereas definitive information on the ability of sunscreens to protect against photocarcinogenesis in humans is not yet available, logic tells us that these sunscreen preparations are highly likely to inhibit photocarcinogenesis and possibly photoenhanced aging in human skin.

The recommendation must be that all persons, particularly those with light skin, should use sunscreens routinely and regularly when spending time exposed to the sun.

NICHOLAS J. LOWE, MD

Kligman LH, Akin FJ, Kligman AM: Sunscreens prevent ultraviolet photocarcinogenesis. J Am Acad Dermatol 1980 Jul; 3:30-35

Lowe NJ, Breeding J: Evaluation of sunscreen protection by measurement of epidermal DNA synthesis. J Invest Dermatol 1980 Mar; 74:181-182

Sayre RM, Marlowe E, Agin PP, et al: Performance of six sunscreen formulations on human skin: A comparison. Arch Dermatol 1979 Jan; 115:46-49

Acyclovir and Herpes Simplex

ACYCLOVIR (acycloguanosine; 9-[(2-hydroxyethoxy) methyl]guanine; Zovirax, Burroughs Wellcome Co.) is emerging as but one of a new generation of specific antiviral chemotherapeutic agents that are potent inhibitors of herpesvirus, the organisms that cause herpes simplex types 1 and 2, herpes zoster and varicella. The selectivity of the drug is due to the fact that cells harboring the herpesvirus contain thymidine kinase, an enzyme that transforms acyclovir into acycloguanosine triphosphate. Uninfected cells lack thymidine kinase and acycloguanosine triphosphate, a potent inhibitor of viral DNA polymerase, forms in herpes-infected cells at 40 to 100 times greater concentration than uninfected cells. The drug has a low index of toxicity for humans. Acyclovir has been licensed by the Food and Drug Administration in both topical and intravenous forms for treatment of a first episode of herpes simplex in both healthy and immunocompromised patients.

Double-blind controlled trials of topical acyclovir in primary genital herpes have shown a shorter period of viral shedding, less pain and faster healing of lesions compared with findings in controls. No significant difference was observed in these data, however, in patients with the recurrent form of herpes simplex. Because of this and the potential for resistant strains of the virus emerging, it has been advised that acyclovir not be given topically for recurrent genital herpes.

Preliminary studies of orally given acyclovir have generally shown reduced periods of viral shedding, time to crusting and time to complete healing in patients with primary herpes simplex. But whereas symptomatic recurrences of herpes can be successfully suppressed by taking the drug, oral administration of acyclovir did not prevent later recurrence of disease. Intravenous use of acyclovir is selectively indicated for treating a severe first episode of herpes because viral shedding is reduced from an average of eight to two days; likewise, the drug represents a substantial advance in the care of immunosuppressed patients with the recurrent form of mucocutaneous herpes.

STANLEY M. BIERMAN, MD

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Corey L, Benedetti JK, Critchlow CW, et al: Double-blind controlled trial of topical acyclovir in genital herpes simplex virus infections. Am J Med (Symposium on Acyclovir) 1982 Jul 20; 73(1A):326-334

Fiddian AP, Halsos AM, Kinge BR, et al: Oral acyclovir in the treatment of genital herpes—Preliminary report of a multicenter trial. Am J Med (Symposium on Acyclovir) 1982 Jul 20; 73(1A):335-337

Straus SE, Smith HA, Brickman C, et al: Acyclovir for chronic mucocutaneous herpes simplex infection in immunosuppressed patients. Ann Intern Med 1982 Mar; 96:270-277

Diagnosis of Primary Melanoma

ALTHOUGH it is much feared, malignant melanoma is almost completely curable if diagnosed early. Fortunately it most often occurs in superficial locations and has a characteristic appearance. It generally arises de novo on otherwise normal skin, albeit a significant number of lesions arise in preexisting nevi. There are several useful clinical signs that should alert a physician to the possibility of such a tumor. These include changes in size, border and surface and irregular color.

Any irregularly pigmented lesion is suspicious. Most superficial spreading melanoma, which accounts for more than 70 percent of such lesions, will show not only brown and black but also varying shades of red, white and blue. White relates to areas of regression in a tumor, whereas red is due to inflammation. Blue discoloration is more ominous because it suggests pigment present deeper in the dermis. Nodular melanoma is often uniformly bluish black, slate gray or bluish red. Early in their course, lentigo maligna melanoma and acral lentiginous melanoma often have only enlarging brownish discoloration and later show the other characteristic colors.

Most melanoma spreads slowly on the surface of the skin. The initial erratic growth creates an irregular border. The periphery of the lesions is angulated, indented or notched. This is often the first clue. An exception is nodular melanoma, which is smooth margined.

Irregularity of surface is also seen in relatively early lesions. Areas of scale or alteration in surface skin markings may be noted. Most benign nevi are less than 1 cm in diameter. Lesions larger than this or those showing any of the above signs are suggestive.

If diagnosed early, melanoma is amenable to curative surgical treatment more limited in extent than previously thought. Waiting for the late signs such as bleeding, crusting, ulceration or nodule formation will result in a poor prognosis.

R. KENNETH LANDOW, MD

Mastrangelo MJ, Rosenberg SA, Baker AR, et al: Cutaneous melanoma, *In* DeVita VT Jr, Hellman S, Rosenberg SA (Eds): Cancer: Principles and Practice of Oncology. Philadelphia, JB Lippincott, 1982, pp 1124-1170

Sober AJ, Fitzpatrick TB, Mihm MC Jr: Primary melanoma of the skin: Recognition and management. J Am Acad Dermatol 1980 Mar; 2:179-197

Kaposi's Sarcoma: Current Trends

IN 1872 Moritz Kaposi described the occurrence of smooth reddish skin nodules in six men. The characteristics of the disease, later to be named Kaposi's sarcoma, included a predilection for the lower extremities, multifocal presentation with lesions in the viscera and histologic features characterized by hemorrhage and hemosiderin deposition. This classic form of Kaposi's sarcoma is now known to occur most frequently in elderly men of Italian or Jewish descent and to be characterized by chronic indolent nodules on the lower extremities accompanied by lymphedema.

Almost 100 years after Kaposi's original description, two other groups were found to be susceptible to this disease. Kaposi's sarcoma occurs relatively frequently in equatorial Africa, accounting for 9 percent of malignant conditions in Uganda. In addition to the indolent variety, several aggressive forms with extensive lymph node involvement have been identified in African blacks. A similarly fulminant type of Kaposi's sarcoma has been described in patients with renal transplants and in those receiving immunosuppressive therapy.

In July 1981 the Centers for Disease Control reported cases of Kaposi's sarcoma among homosexual men. Many patients were reported to have had an illness characterized by fever, weight loss and lymphadenopathy preceding the appearance of skin lesions. This fulminant form of Kaposi's sarcoma is occurring in persons with immunosuppression as manifested by cutaneous anergy, the presence of opportunistic infections such as *Pneumocystis carinii* pneumonia, lymphopenia and a decreased ratio of circulating T helper-to-T suppressor lymphocytes. A similar syndrome has been identified in Haitians and intravenous drug abusers.

The current epidemic has sparked numerous investigations. The neoplastic cell is probably derived from vascular endothelium as has been shown by immunoperoxidase staining for factor VIII, a vascular endothelial marker. In addition, a pathogenic role for cytomegalovirus has been suggested by the finding of cytomegalovirus antigens in tumor tissue by immunofluorescence and by the identification of cytomegalovirus RNA in tumor cells by in situ cytohybridization. This epidemic provides a unique opportunity to further in-

vestigate the relationship between genetics, environment, immunology, cancer and infections.

Clinicians should be alert to the current epidemic. Skin lesions can present as single or multiple reddish purple macules, nodules or plaques on any location of the skin or mucous membranes. Unlike classic Kaposi's sarcoma, the upper torso and upper extremities may be predominantly afflicted. These lesions may resemble hemangioma or dermatofibroma so that histologic examination is necessary to establish a diagnosis.

ROBERT L. MODLIN, MD

Haverkos HW, Curran JW: The current outbreak of Kaposi's sarcoma and opportunistic infections. CA 1982 Nov/Dec; 32:330-339
Safai B, Good RA: Kaposi's sarcoma: A review and recent developments. CA 1981 Jan/Feb; 31:2-12

Ketoconazole

KETOCONAZOLE IS A new antifungal drug that may become the drug of choice for the treatment of most fungal infections. It is effective against a wide range of mycotic diseases. Its broad spectrum of activity, the ease and convenience of oral administration, its safety and its lack of resistance by an organism indicate a potential unequaled by other drugs and modalities.

Ketoconazole is an imidazole that inhibits ergosterol synthesis by interrupting the demethylation of lanosterol. The drug is fungistatic and appears to be synergistic with host cells. It is indicated for treatment of blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, chromomycosis and paracoccidioidomycosis. Further, it is effective in treating the entire spectrum of dermatophyte infections, pityriasis versicolor and mycetoma due to *Petriellidium boydii*. The drug is also effective in treating leishmaniasis. Because gastric acidity is required for dissolution, antacids, anticholinergics and hydrogen-2 blockers such as cimetidine should not be given concomitantly. They may be administered two hours after ketoconazole. An achlorhydric patient should be given a 200-mg ketoconazole tablet dissolved in 4 ml of aqueous solution of 0.2N hydrochloric acid. The solution can be added to fruit juice and drunk through a straw, followed by a cup of tap water.

The drug has not been shown to interact with oral anticoagulants or hypoglycemic agents nor has it shown carcinogenic or mutagenic effects. It has some teratogenicity when given to rats at ten times the dose for humans.

Adverse reactions have been rare and usually mild, of a nature seldom causing cessation of therapy. In rare instances idiosyncratic hepatitis has been reported to occur, with a possible incidence of 1 in 10,000 patients. As a result, liver function studies should be considered if therapy is to be prolonged. Even more important, patients should be seen at periodic intervals and their condition clinically evaluated by the prescribing physician. With rare cases of idiosyncratic hepatitis being reported, a physician should check a patient for nausea, weakness, vomiting, abdominal pain or jaundice. Any abnormalities should be further evaluated and reported and the drug therapy discontinued.

Ketoconazole also lowers the serum testosterone level and depresses adrenocorticotropic hormone stimulation. At the recommended dosage, however, this is not significant, and the levels return to normal within 24 hours. Occasionally gynecomastia has been reported to occur in male patients who have been receiving long-term therapy; it is transient, however, an escape phenomenon of gland function, and disappears even with continuation of therapy.

In summary, ketoconazole is an effective broad-spectrum antifungal agent that has the convenience of oral administration and rare side effects. No resistant organisms have been reported, despite more than eight years of worldwide use.

PAUL H. JACOBS, MD

Borgers M: Mechanism of action of antifungal drugs, with special reference to the imidazole derivatives. Rev Infect Dis 1980 Jul-Aug; 2: 520-534
McNair A, Gascoigne E, Heap J, et al: Hepatitis and ketoconazole therapy. Br Med J 1981 Oct 17; 283(6298):1058
Stamm AM, Dismukes WE: The role of ketoconazole in antifungal therapy. Drug Therapy 1982 Sep; 12:97-112
Symoens J, Moens M, Dom J, et al: An evaluation of two years of clinical experience with ketoconazole. Rev Infect Dis 1980 Jul-Aug; 2(4): 674-687
Urcuyo FG, Zaias N: Oral ketoconazole in the treatment of leishmaniasis. Int J Dermatol 1982 Sep; 21(7):414-416

Immunotherapy and Bleomycin in the Treatment of Recalcitrant Warts

HUMAN WARTS are caused by species-specific 55-nm large DNA icosahedral papillomaviruses of at least eight different antigenic subtypes. The host response to wart infection involves both humoral and cell-mediated immune responses, but the cell-mediated system seems particularly important in the phenomena of wart rejection and spontaneous regression.

In a recent review of the immunobiology and treatment of warts, Rees notes that a safe and effective vaccine, while long awaited, is still unavailable and that research on wart viruses continues to be hampered by the lack of suitable culture techniques and the difficulty of finding a virus in most types of warts. Moreover, the spontaneous regression of warts in about two thirds of all cases within two years of inception reinforces the fact that aggressive treatment should be reserved for long-standing infections truly recalcitrant to traditional treatment modalities. Two relatively recent and effective modes of therapy, one involving the induction of cell-mediated immunity and the other the direct inoculation of an antimetabolic substance, are described below.

Dinitrochlorobenzene is a potent sensitizer and a known mutagen but is not carcinogenic. Treatment involves sensitization via topical application of a 1 percent to 2 percent concentration of dinitrochlorobenzene in acetone solution and subsequent repeated applications of weaker concentrations (0.05 percent to 0.5 percent) of dinitrochlorobenzene in acetone or aquaphor solution to all involved sites at daily to weekly intervals. Sanders and Smith reported that the above approach resulted in complete clearing in more than 80 percent of patients with warts resistant to standard therapy. The major side effects are local erythema and irritation at the site of application of the dinitrochlorobenzene.

Another highly effective treatment for resistant warts

is the intralesional injection of bleomycin sulfate. In a series involving more than 1,000 warts, Shumack and Haddock found a 93 percent cure rate within four weeks. A 0.1 percent solution was used, with the volume limited to 0.1 ml in any individual site, with no total dose larger than 2 mg. The major side effects are moderate local pain and burning at the injection site and local pigmentary changes.

These two treatments are important additions to the armamentarium of therapy for recalcitrant human warts. They each have above-average cure rates but should nonetheless be reserved for carefully selected cases because they are not without drawbacks in terms of cost and discomfort to patients.

LYLE J. RAUSCH, MD, PhD

Dahl MV: Host defense: Herpes, warts, and other virus infections, chap 9, Clinical Immunodermatology. Chicago, Year Book Medical Publishers, 1981, pp 123-126
Rees RB: Warts—A clinician's view. Cutis 1981 Aug; 28:175-180
Sanders BB, Smith KW: Dinitrochlorobenzene immunotherapy of human warts. Cutis 1981 Apr; 27:389-392
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Pemphigus: An Autoimmune Mucocutaneous Disease

PEMPHIGUS IS AN intraepidermal blistering disease occurring on skin and mucous membranes (for example, the mouth, esophagus and vagina). It is the result of loss of normal cohesion between epidermal cells. The findings of recent studies in two aspects of pemphigus have important clinical implications: compelling evidence suggesting the pathogenetic role of pemphigus autoantibodies and evidence of drug-induced pemphigus.

The evidence supporting the pathogenetic role of the pemphigus autoantibodies has been the correlation of pemphigus antibody titers in serum and the activity of the disease; the observation of neonatal pemphigus passively transferred from an affected human mother, and the finding that organ cultures of specimens of normal human skin in the presence of pemphigus antibody developed histologic changes similar to that of naturally occurring pemphigus. Added to the above evidence is the report in 1982 of success in passive transfer of pemphigus from human to laboratory animals. The results of the experiments using intraperitoneal injection of neonatal mice with various concentrations of serum from patients with pemphigus indicate a direct relation between the degree of acantholysis with the titer of pemphigus antibody. In 1982 the antigen(s) to which pemphigus antibodies bind has been characterized as a cell-surface glycoprotein synthesized by human and mouse keratinocytes. Thus, investigations in recent years have convincingly established pemphigus as an autoimmune disease.

The in vitro studies in recent years also provide a great deal of evidence suggesting that pemphigus antibody, in the absence of complement, activates a proteolytic enzyme(s) that in turn causes the destruction of normal cell-to-cell cohesion. Pemphigus appears to be a unique type of autoimmune epidermal injury that does not require the participation of complement.

The clinical importance of these new findings is that the therapy should be directed primarily at reducing the level of pemphigus antibody in affected patients. The administration of systemic corticosteroids and immunosuppressive agents is (still) the treatment of choice. Other modalities of reducing pathogenetic antibodies such as plasmapheresis have been attempted and require further investigation.

D-Penicillamine-induced pemphigus has been increasingly observed—49 cases have been reported in the literature, most of them in the past five years. These cases have characteristic histologic and immunofluorescent features of pemphigus and a close time sequence between the penicillamine administration and the onset of the disorder. This is another example of a drug-induced autoimmune disease though its mechanism is unknown at the present time. The widespread use of penicillamine for connective tissue disorders indicates the monitoring of its side effects should include pemphigus.

CHUNG-HONG HU, MD

Anhalt GJ, Labib RS, Voorhees JJ, et al: Induction of pemphigus in neonatal mice by passive transfer of IgG from patients with the disease. N Engl J Med 1982 May 20; 306(20):1189-1196
Hu CH, Michel B, Schiltz JR: Epidermal acantholysis induced in vitro by pemphigus autoantibody—An ultrastructural study. Am J Pathol 1978 Feb; 90:345-361
Stanley JR, Yaar M, Hawley-Nelson P, et al: Pemphigus antibodies identify a cell surface glycoprotein synthesized by human and mouse keratinocytes. J Clin Invest 1982 Aug; 70:281-288
Tuffanelli DL: Pemphigus—Medical Staff Conference, University of California, San Francisco. West J Med 1983 May; 138:699-705

Pyoderma Gangrenosum

PYODERMA GANGRENOSUM is an ulcerative skin disorder of unknown cause. Since its description in 1930, little progress has been made in our understanding of the pathogenesis of this disease. However, cumulative clinical experience has provided much information about diagnosis, disease associations and treatment.

The earliest recognizable lesion in this disease is an erythematous papule, nodule or pustule. This early lesion subsequently ulcerates and may enlarge rapidly in a few days until arrested by therapy, it may progress for a longer time—from weeks to months—or it may spontaneously involute. An established ulcer is recognized by its edematous, violaceous and serpiginous border. The ulcer enlarges peripherally and is characteristically undermined at the margin of diseased and normal skin. Lesions most commonly affect the lower extremities, though all body sites can be involved. Lesions characteristically develop at sites of trauma (for example, biopsy sites).

An association between pyoderma gangrenosum and ulcerative colitis is well established. When these two disorders occur together the activity of the skin disease usually parallels that of the bowel disease. Associations between pyoderma gangrenosum and classic rheumatoid arthritis, a seronegative rheumatoidlike arthritis and the arthritis of inflammatory bowel disease have been recognized. Other important but less common disease associations include regional enteritis (Crohn's disease), chronic active hepatitis, plasma cell dyscrasia, leukemia and myeloproliferative syndromes. Pyoderma

gangrenosum occurs without an apparent disease association in about half the cases.

The diagnosis is clinical and rests on the morphologic appearance of an ulcer, its clinical behavior and the presence of an associated disease. Histopathologic findings are not diagnostic but provide supportive evidence for a diagnosis. A biopsy in suspected cases is essential to rule out other mimicking disorders (for example, deep mycoses and atypical mycobacterial infections). Immunofluorescent study of biopsy specimens from an ulcer margin has shown perivascular deposition of IgM, C3 and fibrin in a number of cases. The specificity of this finding and its ultimate use as a diagnostic tool have yet to be established.

Local ulcer care, including careful debridement, and elevation and rest of the affected site are important. Antibiotic therapy should be directed at any associated infection; administration of systemic corticosteroids is the most effective form of treatment. High doses of prednisone, in the range of 80 to 120 mg a day, are frequently required. Sulfones and sulfapyridine are useful for treating steroid-resistant disease or for use as steroid-sparing agents in chronic recurrent disease. Clofazimine, an antimycobacterial agent with antiinflammatory properties, and immunosuppressive agents, particularly azathioprine, have also been used successfully in recalcitrant cases.

ROBERT A. SNYDER, MD

Holt PJ, Davies MG, Saunders KC, et al: Pyoderma gangrenosum: Clinical and laboratory findings in 15 patients with special reference to polyarthritis. Medicine (Baltimore) 1980 Mar; 59(2):114-133

Newell LM, Malkinson FD: Commentary: Pyoderma gangrenosum. Arch Dermatol 1982 Oct; 118:769-773

Warts Are Important, Too

HUMAN PAPILLOMAVIRUS is capable of producing a number of clinically distinct epithelial neoplasms. Previously these clinical characteristics were thought to be determined by the anatomic site where the wart developed, rather than by the virus itself. With improvements in immunofluorescence and immunoperoxidase technology, it appears that there are as many as eight immunologically distinct human papillomaviruses. To a large extent, their antigenic differences reflect their clinical appearance. For example, papillomavirus types 1 and 4 are associated with plantar warts, type 2 with common warts, type 3 with flat warts, type 6 with genital warts and type 7 with butcher's warts.

Papillomavirus type 5 is associated with a rare familial disease called epidermodysplasia verruciformis. In those afflicted, warty neoplasms develop over much of the skin. These tumors tend to degenerate into squamous cell carcinoma. Recently, using DNA hybridization techniques, DNA sequences characteristic of papillomavirus type 5 have been found in a number of squamous cell carcinoma lesions from such patients.

Others have linked genital warts (type 6) with cervical cancer. On the basis of histologic evidence, an unusual condition of the cervical epithelium has been described that is believed to be due to a "subclinical infection" by the papillomavirus. There is compelling statistical evidence that this histologic change is causally related to cervical neoplasia.

Bowenoid papulosis of the genitalia is a newly recognized neoplasm consisting of multiple 3- to 10-mm pigmented papules on the external genital. Because of its disturbing histologic appearance, there is concern over its malignant potential. Both ultrastructural and immunologic evidence has recently pointed to the existence of papillomavirus in these lesions.

Further investigation into host-parasite relationships in papillomavirus-induced neoplasms should be productive. At the very least, we have learned that the wart is not in the least bit "common."

GARY W. COLE, MD

Bunney MH: Viral Warts: Their Biology and Treatment. New York, Oxford University Press, 1982

Kimura S: Bowenoid papulosis of the genitalia. Int J Dermatol 1982 Oct; 21:432-436

Lutzner M, Kuffer R, Blanchet-Bardon C, et al: Different papillomaviruses as the causes of oral warts. Arch Dermatol 1982 Jun; 118:393-399

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Reid R, Stanhope CR, Herschman BR, et al: Genital warts and cervical cancer—I. Evidence of an association between subclinical papillomavirus infection and cervical malignancy. Cancer 1982 Jul 15: 50:377-387

Dysplastic Nevus Syndrome

DYSPLASTIC NEVI were first reported to occur in association with familial malignant melanoma, which accounts for 1 percent to 6 percent of the total cases of melanoma. The presence of such atypical nevi has been designated the "B-K mole" syndrome based on the initials of the surnames of two families originally studied. These lesions occurred in 18 of 20 (90 percent) patients with familial melanoma and 24 of 43 (56 percent) first-degree relatives. Since this report, the occurrence of dysplastic nevi has also been observed in patients with nonfamilial melanoma. As clinical and histologic features of dysplastic nevi in a familial or sporadic context are similar, the following nomenclature has been proposed: dysplastic nevus syndrome, sporadic type, or dysplastic nevus syndrome, familial type. Recognition of such precursor lesions to melanoma may serve to identify patients at risk for this malignancy. Careful follow-up with photographic documentation and biopsy of lesions suggesting malignant transformation are important so that lesions may be surgically removed at an early, curable stage.

Characteristically, dysplastic nevi are larger in size (more than 5 mm) than ordinary acquired nevi and have an irregular color and outline. Although shades of tan or brown predominate, there may be pinkish hues and slight scaling depending on the degree of inflammation. Dysplastic nevi range in number from a single lesion to 200 or more, and occur on covered as well as sun-exposed areas of the body. Lesions continue to develop throughout adult life. Histologic features include atypical intraepidermal melanocytic hyperplasia, dense dermal lymphocytic infiltration with fibroplasia and increased vascularity.

A polygenic inheritance of precursor nevi has been proposed because of the large number of affected persons in melanoma-prone families and the high fre-

quency of sporadic atypical moles occurring in up to a third of cases of nonfamilial melanoma. A transition between ordinary and precursor nevi has been considered; environmental factors may play a role in their expression. Such factors may include ultraviolet light, hormonal changes or alterations in host immunity. The report of melanocytic atypism occurring in pigmented macules on the buttocks following photochemotherapy for psoriasis with psoralen and ultraviolet-A (ultraviolet light in 320- to 400-nm wavelength range) raises the concern that dysplastic nevi may be produced. The influence of immunologic factors is suggested by the rapid development of invasive melanoma in 14 immunosuppressed renal transplant recipients, of whom seven showed dysplastic nevi. ELIZABETH A. ABEL, MD

Elder DE, Goldman LI, Goldman SC, et al: Dysplastic nevus syndrome: A phenotypic association of sporadic cutaneous melanoma. Cancer 1980 Oct 15; 46(8):1787-1794
Greene MH, Young TI, Clark WH Jr: Malignant melanoma in renal-transplant recipients. Lancet 1981 May 30; 1(8231):1196-1199
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Reimer RR, Clark WH Jr, Greene MH, et al: Precursor lesions in familial melanoma. JAMA 1978 Feb 20; 239(8):744-746
Rhodes AR, Harrist TJ, Stern RS, et al: The PUVA lentigo: Increased number of large, dopa-positive melanocytes (abstr). J Invest Dermatol 1982 Apr; 78:357

Naturally Acquired Leprosy in Animals

BECAUSE OF changing patterns of immigration, leprosy is becoming more common in the United States. This increase has resulted in a number of articles designed to stimulate an awareness in practicing physicians of leprosy as a diagnostic possibility in their patients. In addition, leprosy has been found to occur spontaneously in animals.

For many years leprosy, like smallpox or chickenpox, was considered to be transmitted exclusively from humans to humans, without animal reservoirs. Beginning in 1974 a lepromatous leprosylike illness was recognized in feral armadillos *(Dasypus novemcinctus)*. This illness was identical to that seen in captive armadillos inoculated with human *Mycobacterium leprae* and the etiologic agent could not be distinguished from human *M leprae*. In Louisiana examination of tissues from more than 1,000 armadillos showed rates of infection ranging from 4 percent to 30 percent. Infected armadillos have also been identified in Texas and in the San Diego Zoo in California. A survey of 451 armadillos in Gulf Coast counties of Texas found an overall infection rate of 4.6 percent, range 0 percent to 15.4 percent (Dr Jerome Smith, personal communication). A study by the Centers for Disease Control found no association between leprosy patients in Louisiana and exposure to armadillos. However, a case of lepromatous leprosy was diagnosed in a patient who had killed and dressed an armadillo.

In 1977 naturally acquired lepromatous leprosy was recognized in a chimpanzee. In 1979 a lepromatous leprosylike illness was identified in a "sooty" Mangabey monkey captured in Nigeria. Subsequently lepromatous leprosy developed in captive sooty Mangabey monkeys following inoculation with human *M leprae* harvested from armadillos. Also bacteria from the index case have produced lepromatous leprosy when inoculated into armadillos and other sooty Mangabeys.

Thus there is little reason to doubt that lepromatous leprosy may occur naturally in animals. The importance and significance of these observations are not settled. The possibility that these animals acquired their disease from human material cannot be excluded. However, it also cannot be excluded that these illnesses were acquired from other animals or from the soil. The case of the armadillo dresser suggests that transmission may occur from animal to human. Thus, the old concept that leprosy is exclusively transmitted from human to human is being challenged. THOMAS H. REA, MD

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Carbon Dioxide Laser Treatment in Dermatology

THE CARBON DIOXIDE LASER is being used increasingly in clinical dermatology. The following is a brief description of the properties that make the instrument particularly well suited for specific dermatology applications.

The term laser is an acronym for *l*ight *a*mplification by *s*timulated *e*mission of *r*adiation. The radiation is coherent, meaning that its component waves have a uniform wavelength, are generated in phase and follow an almost parallel path. The carbon dioxide laser emits radiation at 10,600 nm, which is in the far infrared range of the electromagnetic spectrum. The beam target size is 2.3 mm when unfocused and used for tissue vaporization; it is about 0.2 mm when focused and used as a scalpel.

At typically used power settings, exposure times and skin-to-laser distances, the laser beam causes instantaneous vaporization of tissue by heating intracellular water to a temperature of 100°C. This vaporization occurs to a depth of 0.1 to 0.2 mm, and this depth can be varied by adjustment of power settings and exposure times. Hardly any of the thermal energy is scattered from the target to surrounding tissues. This means that only one to two layers of cells adjacent to the vaporized area are damaged by conducted thermal energy. These properties permit the instrument to directly vaporize epithelial lesions or excise them with minimal trauma to surrounding skin and its appendages. Hemostasis is achieved by thermal sealing on impact of vessels up to 0.5 mm in diameter. Nerve endings are sealed in the same way resulting in less postoperative pain compared with other surgical techniques.

The carbon dioxide laser has been applied to the Mohs surgical procedure, a procedure for microscopically controlled excision of skin cancer. A surgeon can choose to vaporize tissue or excise it for frozen-section evaluation; very thin horizontal sections may be removed with minimal artifactual disruption of histologic features and maximal preservation of critical anatomic

areas. Thin layers of cartilage or bone can be removed easily if tumor has invaded these structures. Lymphatics and small vessels are sealed automatically, helping to prevent tumor spread.

Port wine stains and other vascular skin abnormalities are well suited for carbon dioxide laser treatment. In carefully selected patients, laser therapy selectively coagulates and seals the dilated vessels that make up these lesions, sparing the surrounding normal tissue. Before the laser treatment, options were unsatisfactory.

Tattoos respond poorly to removal attempts using dermabrasion and surgical excision, but the laser is sometimes more successful. Pigments that extend into the dermis are selectively vaporized. Again, because of the unique properties of the laser, destruction of normal tissue is minimal, bleeding is negligible, postoperative pain is decreased and scarring is less likely.

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Surgical Treatment of Primary Malignant Melanoma

ALTHOUGH STILL EVOLVING, the surgical treatment of primary malignant melanoma is much less extensive than several years ago. Since 1907 it has been generally accepted that whenever such a lesion is excised, 5-cm borders be removed regardless of depth of invasion. More recent information from several melanoma centers has refuted the need for such generous margins and in fact suggests the adequacy of minimal margins.

A sensible approach to surgical treatment takes into account the depth of invasion as well as the site of the tumor. These take precedence over other factors including the type of melanoma: superficial spreading melanoma, nodular melanoma or lentigo maligna melanoma. Any lesion invading less than 0.85 mm is adequately treated with surgical margins of up to 1.5 cm of clinically normal skin whereas lesions invading more than 1.69 mm are excised with a 3-cm margin. The location of tumors 0.85 to 1.69 mm thick determines their treatment. Such lesions arising in higher risk sites—the upper back, posterolateral arms, posterior and lateral neck and posterior scalp—are treated by taking larger margins whereas lesions up to 1.69 mm thick in any other site are treated by the more conservative excision. Whether or not to remove underlying fascia is an area of controversy; recent evidence suggests it is not necessary. There are proponents of the use of grafts, flaps and primary direct closure. Again the evidence seems to indicate that the less scarring procedures are satisfactory.

There is no consensus regarding node dissection. The most recent prospective studies show no improvement in survival for those who undergo node dissection at the time of initial surgical procedure compared with those who have dissection only when clinically palpable nodes develop. Although initial studies showed a tendency toward slightly improved survival with node dissection in those with deep melanoma, no statistically significant difference was found. On longer term follow-up even this tendency was not apparent. Therefore the most recent evidence indicates prophylactic node dissections are unnecessary.

These more limited surgical guidelines do not unfavorably affect prognosis. As the surgical techniques for melanoma come under closer scrutiny, further changes in recommendations will be forthcoming.

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Editorials

Osler—A Fading Tradition in Medicine?

ELSWHERE IN THIS ISSUE John Geyman calls attention to the Oslerian tradition in medicine and reminds us of the important influence Sir William Osler had upon the development of medical education in this nation. He also traces the all too apparent decline of this tradition in the face of growing specialization and subspecialization in patient care. Not only is the art and science of medicine becoming compartmentalized into specialties and subspecialties, but too often patients themselves are in effect being compartmentalized for their care. As these developments have occurred, the Oslerian role model in medical education has largely given way to the newer role model of a research oriented specialist or subspecialist. The effect this has had on the medical profession and its ever more specialized members has likely been profound, and not in every way beneficial either to patients or to the profession, at least in the view of the public.

Geyman sees today's renaissance of interest in general internal medicine, general pediatrics and of course family practice as offering an instrument for the revival of the Oslerian tradition in patient care and a return of the Oslerian role model in medical education. This would seem well worth the attention and consideration of those who are responsible for formulating the content and developing the ambience of these programs, which are in many ways relatively new in today's firmament of undergraduate and graduate medical education.

—MSMW

Weeds in the West

GENERATIONS OF PIONEERS have migrated westward across the North American continental divide to create a new life away from past religious or political suppression, hard economic realities, family problems or personal anguish. Few achieved or surpassed their greatest expectations, most found some degree of happiness in their adopted homes and some found only disappointment. Regardless of expectations, however, the natural glory of the western landscape cannot fail to be an enriching experience. The first view of golden fields of grass reflecting the summer sun on California and Oregon hills dotted with black oaks, or of the commanding presence of red cedars of the Pacific Northwest or of wind-shaped cypresses on the rocky Monterey coast brings tears of joy to many newcomers.

For some, though, these tears accompany the itchy eyelids, suffused conjunctivae, congested nasal mucosa and paroxysmal sneezing of allergic rhinitis. The visual pleasures of graminae, *Quercus, Thuja* and Cupressaceae would not be possible without the reproductive function of their airborne pollen.

The westward migrants include a fair number of souls from the eastern seaboard and Midwest who have made the trip west in part to escape ragweed hay fever, which they had suffered with regularity each year from the 15th of August to the first frost. West of the Rockies ragweed is virtually nonexistent as a significant allergenic plant, with the notable exception of the Wenatchee Valley apple-growing area of Washington. After the first delightful sneeze-free autumn in the West, however, many *Ambrosia*-sensitive allergic patients discover that they must contend with their previously unexpressed allergies to dozens of western weeds, grasses and trees. The trade-off from six weeks of intensive late-summer allergy is sometimes a year-round succession of long, overlapping pollen seasons. Furthermore, allergy sufferers, like their nonatopic cohorts, often prefer the big city life even in the West, subjecting their already inflamed mucous membranes to the further insult of automobile exhaust fumes, industrial pollutants, smoke and dust.

Dr Geraldine Freeman in this issue calls attention to a potential new allergenic pollen—marijuana. It is no secret that large, albeit illegal, fields of marijuana are being cultivated and harvested, and the allergenicity of *Cannabis* pollen has been recognized for years by allergists, particularly in Iowa and neighboring states where hemp is a natural weed. The finding that a high proportion of allergic patients in southern Arizona have marijuana sensitivity is therefore not surprising. It is not clear yet whether these same patients have symptomatic marijuana pollen allergy. Ongoing pollen surveys are needed to correlate the atmospheric pollen load with seasonal symptoms in skin test-positive patients to determine the clinical significance of marijuana pollen as an aeroallergen. Unfortunately unequivocal identification of this pollen is difficult, because it is delicate and susceptible to morphologic change in dry air.

Marijuana growers are not likely to abandon their lucrative enterprise simply because their product is a potential hazard to some people with allergy. "Harvesting" of the plants by law enforcement agents may not eliminate the crop if self-seeding occurs. This in fact is what happened in the well-intentioned but unsuccessful ragweed eradication programs carried out in the past in several eastern cities.

The pathogenesis of atopic allergy is the subject of much active research at the present time. In addition to the release of membrane-bound histamine from mast cells sensitized with IgE antibodies, leukotrienes synthesized via the lipoxygenase pathway from arachidonic acid and chemotactic factors independent of the complement system are clearly involved in the mediation of atopic allergic inflammation. Knowledge of the

chemical structure and biologic activity of these mediators is extensive and growing rapidly.

The cause of atopy, however, remains unknown, and relevant information is scanty. The IgE antibody—mast cell—mediator effector pathway of the immune response is not unique to allergy but exists and presumably functions in some desirable fashion in everyone. It is an effective system of immunity to certain metazoan parasites. It may act to localize other immune reactants in tissues—that is, the "gatekeeper" concept. A possible role in natural immunity to cancer has even been suggested. What distinguishes an atopic person is the relative ease with which IgE antibodies are made to low-dose natural exposure to atmospheric antigens, as shown once again by the report of Dr Freeman. The finding of a probable immune-response gene for allergy to a purified ragweed allergen and the well-known familial clustering of atopic cases establish the importance of genetic factors. However, the precise phenotypic expression of the atopic abnormality and the reason for different target-organ susceptibilities among different atopic patients remain to be discovered.

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Insulin Therapy: Past, Present and Future

IN THIS ISSUE of the journal, the treatment of diabetic patients with insulin is clearly and aggressively addressed. As one ponders the past, present and future of insulin therapy, one might even subtitle such a monograph "From Art to Science—and Back to Art." Clearly, in the 1920s and 1930s the use of the early therapeutic insulin preparations represented a fine degree of art based upon little knowledge of the hormone's actions and the pathophysiology of diabetes. The immunoassay revolution commencing in the 1960s saw an explosion of information which led to a very rapid clarification of insulin's dynamics, kinetics, metabolism and actions. Only then was it appreciated that this hormone was essential for the well-being of all of the body's tissues, either directly or indirectly, and that its secretion was extremely rapidly altered by changes of blood glucose concentration. Many beautiful clinical studies showed the rapidity (seconds) with which insulin secretion could change as various glycemic agents and other secretagogues were administered. Insulin, consequently, has been established as a "moment-to-moment" hormone and, by the end of the decade of the 1960s, it became clear that even a finer degree of art in its therapeutic use in diabetic patients would be required to imitate the insulin metabolism that one sees in nondiabetic persons.

This compulsion to restore metabolism in a diabetic patient to near normalcy by more refined methods of insulin administration has been blunted by the lack of convincing universal, broad-based, prospectively obtained clinical evidence that restoration to normal or near normal of the body's metabolism in a diabetic person will insure that the chronic complications of diabetes will be eliminated. Although many scientists and clinicians feel that evidence for the benefits of control has been convincing, it is hoped that the multicenter study (Diabetes Control and Complications Trial) sponsored by the National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases of the National Institutes of Health will provide convincing evidence of the magnitude of benefits.

In the past five years assessments of the degree of glycemic control have been improved by the availability of determinations of glycosylated hemoglobin. A physician (and patient) now have a new tool for assessment, one that provides an overview of the past 30 to 90 days of average blood sugar control. This laboratory procedure provides information beyond that of sporadic blood sugar measurements and assessments of glycosuria. There has been a tendency to equate glycemic levels with metabolic control and new metabolic information suggests that in a diabetic patient it may not be correct to equate normal glucose levels with normal metabolism. There is growing evidence that abnormal tissue metabolism can coexist with normal blood glucose levels.[1] Therefore, it is reasonable to assume that auxiliary measuring systems (for example, assessment of fuel oxidation by indirect calorimetry) could be added to the spectrum of monitoring systems.

The monograph in this issue provides a solid review of the physiology of insulin secretion and action and a variety of alternate insulin-injection regimens that a physician can use in the treatment of a diabetic patient requiring insulin. It also provides a logical strategic plan in that it strongly suggests that physicians and patients wisely establish goals, and that both understand that a specific regimen for each patient can be established with considerable flexibility. Diabetic patients need not lead metronomic, inflexible, boring lives. A second part of a total program must be a diet and meal plan communicated to a patient by a physician or allied health professional, usually a nurse or a nutritionist. A third component of the regimen should be a sensible physical activity program. I am reluctant to use the word "exercise" for so often this brings to mind strenuous or semiheroic gymnastics suitable only for an Olympian. Regular physical activity can be easily incorporated into the daily life scheme of all diabetic patients. Activities such as a short daily walk for a usually sedentary person may be the first step in an evolving program designed to increase activity levels consistent, of course, with any physical limitations.

An often neglected component of the insulin-diet-physical activity program that binds them closely together is education. A patient with diabetes who understands the disease, comprehends how and why therapeutic insulin preparations do what they do and acquires a working knowledge of the fundamentals of nutrition (food stuff quality, quantity and meal distribution) is better able to cope with the minor and major crises of life. Many diabetologists feel this leads to an im-

proved quality of life with perhaps lesser frequency of acute complications of diabetes (such as hypoglycemic episodes) and even chronic complications (microvasculopathies and macrovasculopathies). Once again, solid data in this respect are hard to establish.

Science and technology have in the past decade had a major impact on insulin therapy. A substantial number of small portable pumps designed for continuous subcutaneous insulin infusion have appeared, each new generation being more flexible and smaller than the last.[2] In addition, as outlined by Dr Riddle, various devices and materials for self-monitoring of the degree of glycemic control have emerged. During the past few years, studies assessing implantable insulin delivery systems have been started[3,4] and within this past year papers from a symposium have been published concerning the possibility of devising implantable glucose sensors that might be a key component in a totally implantable artificial β-cell providing insulin to a diabetic patient in relationship to the glycemia levels.[5]

In addition, numerous laboratories are attempting to devise ways in which β-cell tissue can be implanted into an insulin-dependent diabetic patient.[6] Some of these approaches have been designed to explore segmental pancreatic transplantation, whereas other programs have focused on the possibility of implanting pancreatic tissue or isolated islets from available neonatal tissue. Newer agents and programs designed to reduce rejection of these transplanted tissues are being pursued, some using newer and more potent immunosuppressive agents, whereas other programs are focusing on macroencapsulation or microencapsulation techniques designed to protect the living β-cell or islet tissue from antibodies or cell-mediated rejection.

Finally, very recent studies have provided new evidence concerning the pathogenesis of insulin-dependent diabetes and indicate that it may be more than five years before the development of even impaired glucose tolerance in which abnormal autoimmunity (that is, islet cell antibodies) can be detected.[7] If further studies confirm that there is an extended period in which a person is a "pre" insulin-dependent diabetic patient, it is conceivable that immune intervention might be applied during this stage. If our concepts of the pathogenesis of insulin-dependent diabetes mellitus are correct and our immune intervention successful, then the possibilities of preventing insulin-dependent diabetes clearly exist.

But until that time that we can prevent this condition, or until there is widely available tissue or device implantation designed to achieve normal metabolism in an insulin-dependent diabetic patient, the programs suggested by Riddle provide a solid basis for treatment of an insulin-dependent or insulin-requiring diabetic patient.

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Ethical Crises and Cultural Differences: A Commentary

OVER THE YEARS, the epidemiologic concept of "indicator strain" has emerged as a valid adjunct to the study of environmental hazards. Briefly, it is based on the observation that frequently the presence of a latent offender will be readily revealed by the way it affects individuals whose vulnerability exceeds that of others, perhaps because resistance either has not had time to develop or has been compromised.

This concept has provided constructive insight into many health problems. An example is the almost universal experience with traveler's diarrhea[1]; others have more tantalizing overtones, pertaining as they do to infections,[2] neoplasms[3] or even the as yet elusive intersection of infection, neoplasia and life-style.[4]

That the concept is not limited to environmental hazards and organic pathology is vividly illustrated by the perceptive study published by Meleis and Jonsen in this issue. Central to the annotated case report is a terminally ill patient around whom the patient's physicians and his family revolve in a complex interplay of human and cross-cultural relationships. A fatal illness abruptly confronts the family with the novel environment of the operational system into which their dying relative is being assimilated. Unaware as they are of the cultural values that permeate the system, they react to the unfamiliar setting as a classical indicator strain capable of pinpointing urgent problem areas for scrutiny or study.

Thus we learn that at the interface between hospital and family, the hospital's needs for informed consent, disclosure of information and termination of life support only heightened the family's mistrust of the professionals and of the system they represented. Meleis and Jonsen believe that this concatenation of events represents more than a simple happenstance brought about by the different cultural background of the patient's family. One can only concur with them, and emphatically so. For some of our own patients, even for some of us, at one time or another, informed consent, disclosure of information and termination of life support have proved to be the very same anguishing hurdles that confronted the unfortunate relatives. Only in their case the entire situation became more fright-

ening and anxiety-ridden because of the rapid pace at which the demands imposed by those three major problems succeeded each other. And, behaving as a sensitive and unfailing indicator strain, the family reacted adversely to each one of them.

The authors also conclude that a universal lesson can be learned from the episode they recount—namely, that it is necessary to comprehend the values and beliefs of patients from other cultures. This is true and suggests that opportunities for anthropologic exposure during the educational process are suboptimal. But I believe that the lesson it teaches goes beyond that. Their study confirms the irreversibility of the emotional chain reactions that may follow inadequate or misconstrued information: in the final analysis what counts is not what was said but what the listener believes he or she has heard.

It is also an illustration of the universal search for a dependable and trusted social support system whenever stress becomes overwhelming. In due time this need was felt on both sides of the operational interface, and each side mobilized what in their eyes seemed most natural: the physicians called for assistance from legal counsel and from the medical ethics committee of the hospital; the dying patient's mother, sister and brothers looked for the backing they needed in time-honored family ties and in the mutual reinforcement they could generate by being physically present in the hospital. However, while communication within sides flowed easily, communication between sides was to become a trying and unsatisfactory experience. In this respect, isn't the microcosm portrayed by Meleis and Jonsen a cogent reminder of the large-scale problems that can be attributed to mismatched communications within a group and among various groups?

Perhaps the case report could even stimulate some interest in a critical evaluation of those otherwise most desirable support systems. In fact one may wonder if some negative ripple effect might not have developed once the lines were drawn. Could the consensus that bolstered the physicians' position have lessened on their part any urge to discuss with the family, even for the mere purpose of discarding them, options lying outside the consensus itself? Conversely, by being around as much of the time as possible and becoming very demanding, could the united front presented by the family have increased the reticence of the hospital personnel? Either event would have further diluted any opportunity for effective communication, especially when a dying patient makes communication increasingly more difficult.[5] Thus Meleis and Jonsen's study is a lesson on the crucial role that should be played by communication, understanding and—why not?—empathy and compassion as well, whenever a catastrophe is impending, and mutual trust risks becoming its first victim. In fact, it would be hard to visualize the rule of mutual trust[6] surviving protracted bilateral lack of communication and what patients and their relatives may perceive as insensitivity to their plight.

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Case Reports

Ciguatera: Caribbean and Indo-Pacific Fish Poisoning

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CIGUATERA, a type of fish poisoning endemic in the Caribbean and Indo-Pacific islands, is characterized by the development of acute gastrointestinal and neurologic symptoms following the ingestion of certain commonly edible reef fish.[1-4] The symptoms are usually transient, but occasionally they persist for weeks or even years.[1,5] This may result in difficulties with diagnosis for physicians in nonendemic areas whose patients have recently traveled. We present two cases seen recently in our travelers' clinic at the University of Washington and summarize the current information on the cause of ciguatera and its clinical spectrum.

Reports of Cases

CASE 1. The patient, a 60-year-old woman, came to the University of Washington Travel and Tropical Medicine Clinic in November 1981 because of fatigue and muscle aches in her legs. She had been in excellent health until mid-October when she and a friend (see case 2) went on vacation to the Caribbean, where they stayed for five days on St Martin and then ten days on Nevis (islands of the West Indies). A month before, while in Nevis, they had a dinner of deep fried fish, fried bananas, a vegetable plate and dessert. About six hours later, the patient awoke with watery diarrhea that persisted for several days. Four days later she noted pruritus, which was particularly severe on her palms, and generalized aching that was especially severe in the thighs and calves. She returned to Seattle but continued to have mild pruritus, severe myalgias and fatigue. She also said that her hands "burned" when she washed them in cold water or took items out of her refrigerator. During the next few days she had the sensation that her tongue was being scalded when she exercised outdoors in cold air. After seeing an internist, who was unable to make a diagnosis, she referred herself to our clinic. Physical examination showed no abnormalities.

CASE 2. The second patient, a 63-year-old woman, was seen in our clinic late in October 1981. She had accompanied the first patient to the Caribbean and had the same fish dinner. The night of the dinner she had awakened with nausea, retching and profuse watery diarrhea. During the next few days she had headache, generalized muscle aches and oral paresthesias when drinking ice water. Itching of her palms and soles developed. The diarrhea abated in seven days, but her muscle aches and general fatigue persisted. Five days after returning from the West Indies, she referred herself to our clinic. Physical examination showed no abnormalities. No treatment was given to either patient, and their symptoms lessened over the next few months.

Discussion

Although fish poisoning was described in the West Indies as early as the 16th century,[5] the first known reference to the name "siguatera" was in 1787 by the Cuban naturalist Parra who described various symptoms that he and his family had following the ingestion of a cooked fish. This name is believed to be derived from "cigua," a local name in the Caribbean for the marine snail *Turbo pica* that supposedly causes similar symptoms on ingestion.[5]

Epidemiology

Ciguatera-type fish poisoning results from the ingestion of a toxin (ciguatoxin) found in certain fish endemic to tropical reefs such as barracuda (Sphyraenidae), red snapper *(Lutjanus bohar),* grouper, amberjack *(Seriola dumerili),* surgeonfish (Acanthuridae), sea bass (Serranidae) and even the moray eel (Muraenidae).[1-4] The toxin, which is concentrated in the liver, digestive tract, reproductive organs and flesh of affected fish, is not inactivated by cooking, freezing or gastric juices.[6,7] There is no easy way to recognize a poisonous fish; taste, texture and odor are unaffected.[1-4]

There is recent evidence to suggest that ciguatoxin originates in the dinoflagellate *Gambierdiscus toxicus* Adachi and Fukuyo.[7] Suspensions of this organism have similar lipid solubilities, chromatographic characteristics and biotoxicity as the ciguatoxin isolated from known toxic fish.[7]

The toxin is thought to be accumulated through the food chain.[1,2,7,8] This is supported by several observations. The first fish to show toxicity within a given area are the herbivorous forms.[7] Nontoxic fish can be made toxic by feeding them fish known to contain ciguatoxin.[8] The larger forms of a given species are more toxic and, when toxic, have on the average higher concentrations of ciguatoxin.[9] This implies that the toxin accumulates as a fish grows.

The nature of this lipid-soluble toxin has been studied.[9-14] It has definite anticholinesterase action, as determined by its acetylcholine action on isolated rabbit intestine, and by its effect on the cholinesterase

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activity in human erythrocytes.[11] This could easily explain such symptoms as bradycardia and mild hypotension. The mechanism of the toxicity is more complex, however, for in rats respiratory failure develops despite administration of atropine or pralidoxime methiodide.[12] Studies on isolated frog and toad sciatic nerve immersed in solutions containing ciguatoxin show a partial inhibition of action potential.[9] This may be due to its ability to increase the passive permeability of the membrane to sodium.[13] It does not appear to affect the sodium-potassium adenosine triphosphatase pump.[14]

Clinical Presentation

Poisoning classically occurs in two to six hours, but the incubation period can vary from minutes to more than 30 hours.[1-4,15-17] The toxicity is variable, and some people may show minimal symptoms on eating toxic fish. The worst reactions tend to occur in people who have had prior ciguatera poisoning,[15] suggesting the development of sensitivity or, more likely, the accumulation of toxin in the body.

Frequently the earliest symptoms are gastrointestinal. Watery diarrhea occurs in 40 percent to 80 percent of cases, and abdominal cramps or vomiting (or both) occurs in nearly half,[1,2,4,15] Some patients have no abdominal symptoms.[17] When abdominal symptoms occur, they usually subside in one to three days.

The neurologic manifestations are the hallmark of the disease. Pronounced dysesthesias or hyperesthesia around the mouth and in the distal extremities is characteristic. The teeth may feel numb or loose. (This has been reported frequently in the literature and was noted in about 25 percent of a series of 3,009 patients from the South Pacific.[15]) Sensory reversal in which cold objects "burn" to the touch was reported in nearly 87 percent of that same series. Visual symptoms of blurring and even transient blindness have been reported.[2,17] Findings on neurologic examination are usually normal but rarely ataxia, paresis or paralysis develops.[18]

Sinus bradycardia and mild hypotension are often seen in severe cases of ciguatoxin poisoning. The few fatal cases appear to be due to coma, convulsions and respiratory depression.[2,15,17] Although the mortality in the earlier literature was recorded as high as 12 percent, most recent series have reported only occasional deaths.[1,2,4,15]

Other clinical manifestations include skin rashes in up to 20 percent, which are typically areas of erythema that blister or desquamate (particularly on the hands and feet).[2,15-17] Pruritus occurs in 10 percent to 45 percent of the cases and usually presents one to three days after the fish is ingested.[4,6,15] These symptoms may persist for days to weeks.[4,6]

Another major feature of ciguatera is the musculoskeletal symptoms of asthenia, cramps, arthralgias and shooting pains in the extremities. The feeling of weakness may persist for months and has been occasionally reported to last for years.[1,2,5,15] Not infrequently the symptoms may return during periods of stress, illness or malnutrition.[2,17]

Fever is distinctly unusual and suggests the presence of another disorder.[6,15]

Diagnosis

Diagnosis is usually made on clinical grounds and is based on the abrupt development of gastrointestinal and neurologic symptoms following the ingestion of bottom-dwelling reef fish.

Besides clinical recognition, there are several methods of assaying ciguatoxin if a sample of the suspected fish is available. The original test was to feed portions of the implicated fish to a cat or mongoose and to look for neurologic symptoms of drowsiness, ataxia, coma or death.[1,2,19] The assay of ciguatoxin has been improved with the extraction of ciguatoxin from flesh via serial elutions with solvents such as acetone, ether and methanol.[2,19] This lipid-soluble, heat-resistant, acid-stable extract can then be tested by intraperitoneal injection in mice, for which it is extremely toxic.[2,9] A bioassay using brine shrimp larvae has also been described.[20] Besides these bioassays, a radioimmunoassay has been developed.[21]

Treatment

If a patient is seen within hours, forced emesis and purgation may help eliminate any remaining toxic fish. The fish should be saved for further analysis. All persons who ingested any part of the fish should be contacted. Treatment is purely symptomatic. Fluid and electrolytes should be repleted if vomiting and diarrhea are severe. Cool showers may relieve the itching.[2] Administration of atropine sulfate has been recommended for the cholinergic symptoms[6,16]; some feel, however, that it may be contraindicated because it can inspissate secretions.[2,17] Similarly, other therapies that have been tried with inconclusive results include calcium gluconate, pralidoxime chloride and pyridoxine hydrochloride (vitamin B_6).[2,16,17]

Differential Diagnosis

Neurotoxic and paralytic shellfish poisoning should be considered because they also cause dysesthesias with nausea, vomiting and diarrhea. Occasionally the paralytic form of shellfish poisoning may result in ataxia, paralysis, respiratory failure and death.[3] However, the dinoflagellates responsible for these entities are most common in waters in latitudes above 30° north and below 30° south, whereas the ciguatera organisms are essentially confined to latitudes between 35° north and 35° south.[2,3] Another entity that should be considered is type E botulism, which is frequently associated with the ingestion of smoked fish and is found most commonly in Alaska and the Great Lakes states. Type E botulism can also present as an acute gastrointestinal illness with nausea, vomiting, abdominal cramps and diarrhea, followed by the onset of neurologic symptoms.[22] Puffer fish poisoning due to tetrodotoxin[1,2,6,17] is another acute gastrointestinal illness with prominent neurologic symptoms most commonly seen in Japan, where these fish are considered a delicacy. Hyperven-

tilation may also produce many of the dysesthesias reported for fish poisoning and should be considered in the differential diagnosis.

Prevention

The highest incidence of poisoning generally occurs around coral reefs that have been recently disturbed.[1,2] This can occur by natural means such as storms or hurricanes or by man-made events such as dredging operations, blasting or waste disposal.[1,2] Reef fish from these areas are especially prone to carry the toxin. In tropical and subtropical island areas one should avoid eating the larger predacious reef fish or the tropical moray eel. Finally, one should never eat the liver, viscera or roe from any tropical fish.[1,2]

As illustrated by these two cases, the problem might be seen by physicians in any part of the world who care for travelers who have been to endemic areas. In addition, with international commerce and modern fish-processing techniques, potentially toxic fish may be sold in inland markets far away from their source.

Addendum

Since this report was written, Engleberg and coworkers[23] described the effects of ciguatera poisoning in a population defined by exposure to toxic fish.

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Alcohol-Related Pain and Hodgkin's Disease

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PAIN ASSOCIATED with alcohol ingestion is a relatively specific, though uncommon, symptom of Hodgkin's disease.[1] The pain, which may develop almost immediately after an alcoholic drink is swallowed, can be very intense and has on occasion caused chronically alcoholic persons to abstain from liquor. This dramatic symptom may be the sole presentation of Hodgkin's disease and occur before there is palpable lymph node enlargement or constitutional symptoms that might otherwise alert an examining physician to the disease. In this setting the recognition of the association of alcohol-related pain with Hodgkin's disease takes on particular importance.

Report of a Case

The patient, a 30-year-old computer salesman, was referred for rheumatologic evaluation because of recurrent right arm pain. He had been in good health until four months before he consulted a physician. At that time he first noted the development of diffuse aching in his right shoulder and arm, which would occur abruptly after a few swallows of beer or hard liquor. The pain would persist for about 30 minutes and then would gradually resolve despite his continuing to imbibe. He had no accompanying swelling or color changes of his arm, weakness or incoordination. He voluntarily tried eliminating alcohol and was free of the pain, only to have it recur with reintroduction of alcohol. Several weeks after the patient's arm pain began, similar aching developed in the left side of his mandible. Despite his alcohol-related pain, the patient continued to drink 3 to 6 oz of alcohol a day. He said he did not have any constitutional symptoms such as fever, night sweats or weight loss, and felt otherwise well.

On physical examination the patient appeared well developed and in good general health. No abnormalities of his right shoulder or arm, neck or mandible were detected. There was no lymphadenopathy or hepatosplenomegaly. Routine blood tests, including an alkaline phosphatase study, showed normal values. A chest roentgenogram showed a poorly defined left mediastinal mass overlying the main pulmonary artery. Chest computerized tomographic scan confirmed the presence of a smooth-bordered mass in the left upper mediastinum. A mediastinal biopsy was diagnostic for nodular sclerosing Hodgkin's disease. A bone marrow biopsy specimen, bone scan and lymphangiogram showed no additional sites of involvement.

En bloc irradiation of the cervical, supraclavicular, axillary, mediastinal and hilar lymph nodes (Mantle

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therapy) was instituted and within two weeks the patient's alcohol-related pain had completely resolved.

Comment

The association between alcohol-related pain and Hodgkin's disease was first noted in 1950.[2] Published surveys that followed reported an incidence ranging from 15 percent to 30 percent.[3,4] More recent observations, however, suggest a much lower frequency in the range of 1.5 percent to 5 percent.[1,5] The decreasing incidence of this symptom has been ascribed either to a possible change in the natural history of the disease or to the fact that patients with Hodgkin's disease tend to be identified earlier.[1,6]

The pain induced by alcohol has been described as either sharp and stabbing or dull and aching. A patient frequently links the discomfort with alcohol ingestion and may voluntarily discontinue its use. Characteristically, the pain begins within minutes after a patient swallows some of an alcoholic drink and subsides within 30 minutes to a few hours. In our patient, the pain subsided despite his continuing to drink.

Retrosternal pain has been noted with mediastinal lymph node involvement whereas with diseased axillary or cervical nodes, pain may be felt in the shoulder, neck or arm. The abdomen and groin are also sites of alcohol-related pain, and back pain with or without radiation down the leg has been described. When disease is present at several sites pain may not be felt in all of them. An important observation is that tumor can invariably be identified at or near the site of the alcohol-related pain, if not at the time of initial presentation, then when relapse occurs.[5]

Several features seem to characterize patients with Hodgkin's disease who have alcohol-related pain. Nodular sclerosing Hodgkin's disease is the predominant histologic type, and a higher than expected incidence of mediastinal involvement has been reported.[3,5] More women than men tend to have this symptom despite a two-to-one male predominance for the disease.[5]

The pathogenesis of alcohol-related pain is not well understood, though it is believed to result from localized swelling with stretching of the capsule of the affected lymph nodes or increased pressure in diseased marrow that expands and produces bone pain. Visible swelling of involved lymph nodes has been observed after ingestion of alcohol in patients with alcohol-related pain and, in at least one instance, thermography recorded a rise in lymph node temperature.

Although alcohol-related pain is uncommon, this report is a reminder that this symptom may precede any other recognizable feature of Hodgkin's disease and consequently may be helpful in the early diagnosis of this potentially curable disease.

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Secondary Syphilis With Pulmonary Involvement

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REPORTS OF CASES of primary and secondary syphilis have been increasing in number in the United States for the past several years,[1] and because of this physicians are rediscovering the protean manifestations of this disease. Pulmonary involvement in acquired secondary syphilis is uncommon.[2] We report the case of a 39-year-old man who had secondary syphilis and bilateral infiltrates on a chest roentgenogram. Following penicillin therapy for syphilis, the pulmonary abnormalities cleared over several months. Clinical criteria for the diagnosis of acquired secondary syphilis of the lung are suggested.

Report of a Case

A 39-year-old homosexual man was seen in August 1980 because of malaise for the past six months and a 5.9-kg (13-lb) weight loss in the previous month. He noted no fever or chills but had frequent night sweats. Four months previously, numerous nonpruritic skin lesions had developed in the groin and spread in a migratory fashion to the abdomen, chest, back, arms, legs and scalp. He smoked two packs of cigarettes per day. He said he did not abuse drugs intravenously or otherwise. He lived with 24 cats in San Francisco and had traveled recently to the Midwest. He had had multiple anonymous sexual contacts during the preceding months. He was currently unemployed but had worked in a grocery store. On review of systems there was a chronic nonproductive cough of two to three years' duration.

It was learned from the Public Health Department that the patient had been treated previously for syphilis. In 1972 his VDRL titer was positive at a 1:4 dilution and he received intramuscularly two injections of 2.4 million units of benzathine penicillin G at an interval of a week. Subsequent serologic testing, shown in Table 1, showed a VDRL titer in 1978 that was positive at a 1:2 dilution with a strongly positive result on fluorescent treponemal antibody-absorption test. In October 1979 his VDRL was positive in a titer of 1:1,024 and he was treated as in 1972. A VDRL titer in June 1980 was 1:128. In early August 1980 it rose to 1:256 and several weeks later it had risen to 1:512.

On physical examination he appeared well developed, was in no acute distress and had normal vital signs. Multiple salmon-colored, indurated, annular 0.5- to

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2-cm macules were scattered over the chest, back, arms and legs. There was no hypoesthesia. The palms and soles were hyperkeratotic without distinct lesions. Marked nontender mobile axillary, inguinal, epitrochlear and femoral lymphadenopathy was present. The lungs were clear. Similar maculopapular lesions without ulceration were seen on the shaft of the penis and on the scrotum. There was no penile discharge. No other abnormalities were detected.

TABLE 1.—*VDRL Titers of a 39-year-old Man With Syphilis With Pulmonary Involvement (San Francisco Public Health Department Records)*

Date	*VDRL Titer*	*Date*	*VDRL Titer*
1972	1.4*	Aug 27, 1980	1:512*
1978	1:2	Dec 1980	1:32
Oct 1979	1:1,024*	Mar 1981	1:16
Jun 1980	1:128	Aug 1981	1:16
Aug 1, 1980	1:256		

*Patient received penicillin therapy.

Laboratory evaluation gave the following results: erythrocyte sedimentation rate, 52 mm per hour; VDRL, 1:512; hemoglobin level, 13.6 grams per dl, and leukocyte count 9,900 per μl with a normal differential count. Chest roentgenograms showed a definite lingular infiltrate and a probable right lower lobe infiltrate (Figure 1, top).

The patient was admitted to hospital for further evaluation. Results of chemistry (SMA-6 and SMA-12) analyses, thyroid function tests and urine analysis were within normal limits. The electrocardiogram showed no abnormalities. Purified protein derivative (5 tuberculin units) and coccidioidomycosis skin tests were negative; *Candida* skin test was positive. Complement-fixation titers were negative for coccidioidomycosis and histo-

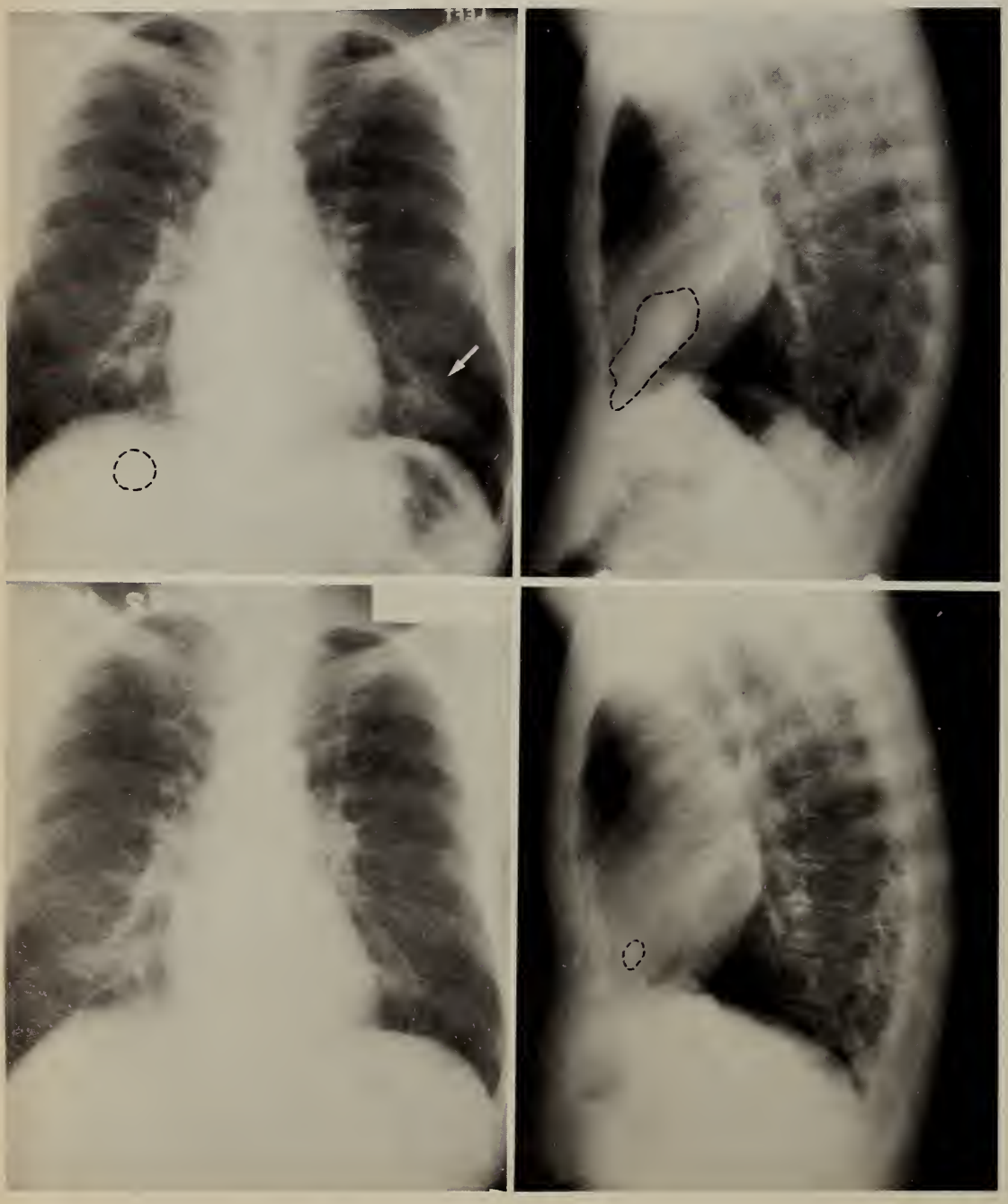

Figure 1.—Top, Chest roentgenogram showing definite lingular infiltrate (**arrow**) and probable right lower lobe infiltrate (**dotted circle**). **Bottom,** Chest roentgenogram four months later showing resolution of right lower lobe infiltrate and nearly complete resolution of the lingular process (**dotted circle**).

plasmin; heterophil and hepatitis B surface antigen test results were negative; and *Toxoplasma* fluorescent antibody IgG test was positive (titer 1:64). Pulmonary function testing showed no abnormalities. The patient produced no sputum for analysis. Analysis of a cerebrospinal fluid specimen, obtained to exclude asymptomatic central nervous system involvement, showed no cells, normal glucose and protein levels and negative results on cytology examination, VDRL test and culture. A biopsy specimen of involved skin showed a round cell infiltrate with a prominent plasma cell component in the papillary dermis, typical of secondary syphilis.

Because of the patient's multiple sexual contacts, we interpreted the fourfold rise in VDRL titer after the previous decline as evidence of luetic reinfection. Benzathine penicillin G, 2.4 million units, was injected intramuscularly and within six hours the patient became febrile to 38.2°C and his skin rash became more erythematous. Within 24 hours the patient's temperature returned to normal and his rash began to fade. Further investigation of the pulmonary infiltrates was deferred pending evaluation of the response to penicillin therapy. His hospital course was otherwise uncomplicated.

Following discharge, the patient's malaise and night sweats resolved and he regained 3.6 kg of weight. The rash cleared by December 1980. A chronic nonproductive cough and minimal lymphadenopathy have persisted. The sedimentation rate returned to normal and the VDRL titer fell to 1:32 by December. Serial chest roentgenograms done in October and December 1980 showed gradual resolution of the pulmonary infiltrates (Figure 1, bottom). The patient refused to return for further evaluation. Subsequent serologic testing by city health authorities recorded a further decline in VDRL titer to 1:16 by March 1981 and persistence of the VDRL titer at that level in August 1981.

Discussion

The first historical description of syphilis is a matter of debate. According to Cleugh,[3] no definite evidence had been found for this disease before 1495, and Smith[4] thought that it was first known around the time of the Reformation (16th century). Initially called by multiple names such as the "French disease," "Italian disease" or "Spanish disease,"[4] its current name is derived from the 1530 poem by Girolamo Fracastoro, *Syphilis sive Morbus Gallicus,* in which the shepherd Syphilus is afflicted with the disease.[3]

Porter[5] in 1885 was one of the first Americans to discuss acquired pulmonary syphilis. Subsequent studies evaluating necropsy specimens from the general population have estimated the prevalence of syphilitic lung disease at 0.55 percent.[6-9] The prevalence in autopsy studies on persons known to have had syphilis varies from 1 percent to 12.5 percent.[6-9]

Discussions of pulmonary syphilis are usually directed to tertiary disease stages. In 1920 Karshner and Karshner[10] remarked that secondary pulmonary syphilis can be "dismissed with a word. In a few of the cases mild bronchitic symptoms date from the period of exanthem." Earlier, Dieulafoy[11] reminded physicians that pleurisy may occur during the secondary stages and that bronchitis may be one of the earliest manifestations of syphilis, but parenchymal disease only appears in the advanced tertiary stages. Claytor[12] reported that the usual time from onset of disease to pulmonary involvement is 5 to 10 years, with cases occasionally noted as early as 1 or as late as 20 years after the appearance of a chancre. Karshner and Karshner[10] described four cases of pulmonary involvement within a year of onset of disease, however, and Olsan and Chambers[8] noted seven cases of early lues with pulmonary involvement. More recently, Biro and co-workers[2] discussed the case of a patient who had secondary syphilis and pulmonary involvement.

Diagnostic criteria for secondary syphilis of the lung are not available. Howard,[6] studying patients who had predominantly tertiary disease, suggested that a diagnosis of pulmonary syphilis should be considered when the following are present: clinical pulmonary involvement occurring without fever, sweats or emaciation; sputum negative for tubercle bacilli; other stigmata and serologic evidence of syphilis. A therapeutic trial is then undertaken. Morgan and colleagues[13] more recently noted that if a patient

> has a suggestive clinical picture, positive serological tests, and a persistently negative sputum for tubercle bacilli, if the radiological lesion clears decisively under antisyphilitic treatment, there are reasonable grounds for diagnosing pulmonary syphilis.

Similar criteria for the diagnosis of pulmonary syphilis, based largely on experience with tertiary disease, have been proposed by Hartung and Freedman[7] and Pearson and DeNavasquez.[14]

Based on the above criteria, we propose that the following be used as guidelines for the clinical diagnosis of secondary luetic involvement of the lung: (1) historical and physical findings typical of secondary syphilis, (2) serologic tests positive for syphilis, (3) pulmonary abnormalities seen radiographically with or without associated pulmonary symptoms or signs, (4) exclusion of other forms of pulmonary disease when possible by findings of serologic tests, sputum smears and cultures, and sputum cytology examination and (5) therapeutic response of radiologic findings to antisyphilitic therapy.

The diagnosis of syphilis in our patient was based on a fourfold rise in VDRL titer, skin lesions clinically and pathologically typical of secondary lues, development of a mild Jarisch-Herxheimer reaction with treatment and a subsequent fall in VDRL titer. Further evaluation elicited no other cause for the pulmonary infiltrates that resolved within several months of the penicillin therapy. This time course is similar to that described by Biro and associates.[2]

Considering the recent increasing incidence and recognition of primary and secondary syphilis (33.4 percent more cases diagnosed in 1980 than in 1977), especially among homosexual men,[15] it is likely that luetic pulmonary involvement will also appear with increasing frequency. Given the potential for diagnostic

confusion with entities such as lymphoma, sarcoid or, among homosexual men, cytomegalovirus infection or *Pneumocystis carinii* pneumonia, the clinical diagnostic criteria we suggest may prove useful.[16]

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Acute Renal Failure Following Repeated Streptokinase Therapy for Pulmonary Embolism

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PREVIOUS REVIEWS[1,2] have described the benefits and risks of administering fibrinolytic agents to bring about clot dissolution in both arterial and venous disease. As activators of the conversion of plasminogen to plasmin, these agents produce major side effects that include varying degrees of hemorrhage. Other complications, particularly with the use of streptokinase, are pyrogenic and allergic reactions, including anaphylaxis.[3] In this report we describe the case of a patient in whom a pyrogenic reaction and acute renal failure developed after he received streptokinase on the second of two occasions for pulmonary embolism.

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Report of a Case

A 38-year-old man was admitted to our hospital because of the recent onset of chest pain. Further history disclosed a contusion of the right calf that was followed by several episodes of localized pain and swelling. On the day of admission, his chest pain and associated symptoms were typical of angina pectoris. On examination in the coronary care unit, the respiratory rate was 40 per minute, the pulse was 88 per minute and the blood pressure was 100/88 mm of mercury. There was no jugular venous distention. The lungs were clear to auscultation. The point of maximal cardiac impulse was not displaced, the first and second heart sounds were normal and a fourth heart sound was present at the apex. No murmurs or friction rubs were audible. Peripheral pulses were normal. The lower extremities were not tender and there was no evidence of edema, erythema or localized calor. The remainder of the examination findings were unremarkable.

An electrocardiogram showed normal sinus rhythm, pronounced left axis deviation, deeply inverted T waves in leads V_1 through V_4, and deep S waves in leads V_5 and V_6. A portable chest x-ray study showed no abnormalities. The hemogram, sedimentation rate, serum urea nitrogen, serum creatinine and analysis of urine gave normal values. An arterial blood gas determination made while the patient was breathing room air showed that the partial pressure of oxygen (Pao_2) was 71 mm of mercury, the partial pressure of carbon dioxide ($Paco_2$) was 28 mm of mercury and the pH was 7.47. Creatine kinase was 107 IU per liter (normal, 225 or less), lactic dehydrogenase was 248 IU per liter (normal, 200 or less) and aspartate aminotransferase (formerly, SGOT) was 28 IU per liter (normal, 41 or less). Serial cardiac enzyme determinations did not suggest an acute myocardial infarction.

During the first two hospital days, angina-like chest pain continued to recur but was relieved by the sublingual use of nitroglycerin. On the third hospital day a cardiac catheterization was done. All right heart pressures were moderately elevated. The pulmonary artery pressure was 59/27 mm of mercury, with a mean pressure of 34 mm of mercury. Pulmonary angiography showed large embolic filling defects in the right and left proximal pulmonary arteries with smaller filling defects in the branch vessels supplying the right and left upper lobes and the left lower lobe. Findings on left ventriculography and coronary arteriography were normal. Streptokinase therapy was begun, with a loading dose of 250,000 units and an hourly infusion of 100,000 units. After two hours there was bleeding from the femoral arterial and venous catheterization sites that could not be controlled. Administration of the drug was discontinued, and continuous infusion of heparin was begun to maintain the partial thromboplastin time in the range of 1½ to 2½ times the control values.

On the 11th hospital day, pain in the patient's right calf, acute chest pain and dyspnea recurred. There was a palpable tender cord in the right popliteal area. An

arterial blood gas determination while the patient was breathing room air showed a Pao_2 of 62 mm of mercury, a $Paco_2$ of 30 mm of mercury and a pH of 7.56. Electrocardiograms continued to show a right ventricular strain pattern. Because of evidence for recurrent pulmonary emboli while receiving heparin and the unavailability of urokinase, streptokinase therapy was reinstituted. Four hours after resumption of the drug, the patient had diffuse myalgias, a fever developed to 40.6°C (105°F) and he had rigors. He had no rash or bronchospasm and was never hypotensive. Coagulation measurements were made and were not significantly different from their control values. Because of no apparent "lytic effect" and the severe febrile response, streptokinase therapy was discontinued and continuous infusion of heparin was resumed at a higher dose. During the next 15 hours the patient was oliguric. No other drug was being administered.

The serum creatinine level rose from the admission value of 1.3 mg per dl to 2.8 mg per dl. The initial serum urea nitrogen level was 28 mg per dl and the leukocyte count rose to 27,000 per cu mm, with a normal differential count and no eosinophils. Multiple blood cultures grew no organisms. The serum creatine kinase value was initially elevated to 443 IU per liter but returned to normal on later tests. The uric acid level was 5.4 mg per dl and did not rise on further measurements. Urine analysis showed many leukocytes and fine granular casts, few hyaline casts and no erythrocytes or erythrocyte casts. Dipstik tests showed 3+ protein and 1+ occult blood. No eosinophils were seen on Wright's stain of the urine. Other studies of the urine showed 13 mEq per liter of sodium, a creatinine level of 26 mg per dl and an osmolality of 279 milliosmole (mosm) per kg of water (normal, 50 to 800). Fractional excretion of sodium was 6.9 percent. During the first 24 hours of his renal failure, the serum creatinine and urea nitrogen tests reached their highest values of 4.8 mg per dl and 57 mg per dl, respectively.

Over the next five days the patient's oliguria resolved. By the 13th hospital day the serum creatinine level was 1.2 mg per dl. The highest serum potassium level reached was 5.8 mEq per liter. Serum calcium concentration fluctuated within a range of 7.7 and 8.5 mg per dl. After a long additional time in hospital, the patient was discharged in good condition on a regimen of oral anticoagulants. Subsequently, renal function findings remained in the normal range with no recurrence of renal impairment.

Discussion

This is not the first instance of acute renal failure being related to the use of streptokinase. Rieben and co-workers[4] reported the case of a 65-year-old man in whom livedo reticularis developed two days after beginning thrombolytic therapy with streptokinase. Following this, necrosis on one foot and acute renal failure developed. The patient died and an autopsy showed severe ulcerative atherosclerosis of the aorta with cholesterol embolization to numerous organs, particularly the kidneys. The close timing between streptokinase infusion and the subsequent clinical findings led the authors to conclude that the thrombolytic therapy contributed to acute diffuse embolization by dissolving the protective thrombi over the ulcerative atheromatous plaques.

A case somewhat similar to ours was reported by Spangen and colleagues[5] in which a 50-year-old man was given streptokinase because of deep venous thrombosis that was progressing despite heparin therapy. Four days after discontinuing treatment with streptokinase, back pain developed, along with glycosuria, hypo-osmolality of the urine and a slight rise in the serum creatinine level. A radionuclide renal scan showed normal glomerular uptake but bilateral postglomerular obstruction. In the ensuing week, his symptoms and laboratory abnormalities resolved and a follow-up renal scan showed no abnormalities. The authors attributed his renal dysfunction to a nonspecific immune reaction.

The precise cause for our patient's acute renal failure was not clear. A biopsy of a kidney could have provided important information but it would have required discontinuation of anticoagulant drugs. Even without a tissue diagnosis, the acute renal failure, as observed in this case, would suggest several possible causes.

Having undergone a cardiac catheterization, the patient could have had a toxic nephropathy due to iodinated radiographic contrast material. However, eight days elapsed before there was any sign of renal insufficiency; thus, this possibility is untenable. Prerenal azotemia might also be considered, but the laboratory results and clinical course following the onset of acute renal failure make this diagnosis unlikely. An attractive hypothesis is that streptococcal antigens precipitated an acute glomerulonephritis. Indeed, an eight-day "latent period" had elapsed from the time of the first streptococcal antigen exposure. In contrast to our patient, however, most persons in whom poststreptococcal glomerulonephritis develops have only vague constitutional symptoms at the time of onset, and fever is unusual.[6] Furthermore, the fractional excretion of sodium militates against the diagnosis of glomerulonephritis.[7] Because the events and laboratory results are more representative of an acute tubulointerstitial process, at least two other causes were considered.

The rigors and high temperature observed in this patient could have caused rhabdomyolysis and acute renal failure. In favor of this diagnosis was the (mildly) elevated creatine kinase level, urine positive for occult blood with no erythrocytes found on microscopic examination, the rapid rise in serum creatinine level and the presence of mild hypocalcemia. Pigmented granular casts were not seen, however, and the serum values for uric acid and potassium were not raised. Nevertheless, myoglobinuric renal failure has been reported to occur under similar clinical circumstances with only modest elevations of serum creatine kinase.[8]

Having been immunologically sensitized with the

first exposure to streptokinase, this patient very likely had a hypersensitivity reaction associated with the streptococcal antigen. With the close relationship to oliguria, an acute hypersensitivity-induced interstitial nephritis and renal failure may be the diagnosis most in keeping with this case. Although the presence of eosinophils in the blood or urine was not observed, this finding is not necessarily required for the diagnosis.[9] As is typical in most cases of acute interstitial nephritis, renal dysfunction resolved after removal of the offending agent.

Summary

Streptokinase may be responsible for acute renal failure on the basis of a hypersensitivity reaction resulting in either an acute interstitial nephropathy or renal failure due to myoglobinuria from nontraumatic rhabdomyolysis. Atheroembolic renal failure may be an operative mechanism in older patients. Given appropriate indications and in the absence of contraindications, there is no reason to deny a patient an initial course of streptokinase. Based on our experience with repeated streptokinase therapy, we would recommend the use of urokinase if a thrombolytic agent is to be used in the context of recent streptokinase administration. Otherwise, alternative measures (for example, vena caval umbrella or clipping) may be a better choice for the management of ongoing pulmonary thromboembolic disease.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgement before publication.

Health Hazards in Industry

TO THE EDITOR: Industrial medicine has been my primary interest for over 25 years, so I was pleased to receive the December 1982 issue of the journal.

I am used to getting strange reactions when asked about my "specialty," as though I have a touch of the blue collar. Not quite so bad, however, as a venereologist I once knew whose hostess, on learning of his calling, followed him around the house wiping the doorknobs.

Unfortunately I got the same feeling after reading your introductory editorial ("The Tip of a Huge Iceberg?").[1] In your effort to upgrade occupational medicine you ignored human factors, which form the basis of our specialty. As several of your contributors pointed out, occupational or industrial medicine has been with us for a very long time. So has our knowledge of the hazards of asbestos. Yet (in discussing one company that sought relief in bankruptcy) you suggest that this is some scientific breakthrough born of young investigators, which is about to tear our social fabric asunder.

As long ago as 1906 British investigators gave evidence of the hazards of asbestos,[2] and the literature has been replete with warnings ever since. With regard to the litigation concerning asbestos I am afraid you have missed the whole point clearly enunciated in *Borel v Fibreboard Paper Products Corporation*.[3] The social evil was that the defendants had a "duty to speak but remained silent." This is not a new social phenomenon but one as old as the garden of Eden—deceit. As long as industry employs such methods we shall require an overburdened legal system to counterbalance them. No doubt this most recent ploy of using Chapter 11 bankruptcy in a solvent corporation will now require the efforts of a host of bankruptcy lawyers to litigate the claim.

One of your contributors notes a code of ethics for occupational physicians. One tenet of his code is that a physician should communicate information about the health hazards of industry. Can you imagine what would happen to an employee physician should he dare to rock the ship of industry—you know well who would perish.

Remember the Titanic ran into the tip of that huge iceberg although her captain had been well and truly warned of the perils. Perhaps the captains of industry should be put on notice of a similar fate should they stay speeding on the same course, disdaining all warnings.

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What Does the Future Hold for Medicine?

TO THE EDITOR: Last week I referred a woman whom I suspected of having a transient ischemic attack (TIA) to a neurologist for his opinion. Today this lady came into my office, boiling with anger: "He saw me for 20 minutes, asked me a few questions, told me to touch my nose, tapped my kneecap and charged me $94.50. That figures out at $5 a minute!"

Remembering the day when I was quite happy to receive $5 for a 45 minute house call I reflected, with sadness, upon what has happened and is happening to the practice of medicine.

The magnitude of these changes and the impact they are exerting on health care in our country are skillfully analyzed by Paul Starr in his new book *The Social Transformation of American Medicine*.[1] This scholarly analysis of the evolution of our system of health care over the past two centuries could be called "The Rise and Fall of the Medical Empire." The author, a youthful Harvard professor of sociology, has done extensive research, and has made an unbiased prognosis of what the future holds for the practice of medicine.

His forecast is not bright. The past 50 years have been the golden years of medicine. Physicians attained virtually complete control of every aspect of medical care. With sophisticated machinery and an almost endless array of drugs we gained new powers to diagnose and treat.

Hospitals, no longer the asylum of the desperately ill or for those in need of surgical treatment as a last resort, now became our medical workshops, subsidized by the government or other third party payors.

The cost of this "progress" has been enormous. Medical fees have soared. Nonprofit hospitals are in the black, and health care corporations are moving in. Open-ended hospital charges are threatened. Individualistic private practice and fee-for-service are facing extinction.

Starr has given us a studious documentation of the past and present history of the practice of medicine as

it evolved to a science and finally to an industry. It is good reading, copiously referenced, carefully indexed, an authoritative look at the past, present and future of health care in America.

One conclusion is unmistakable: The day of the $5 a minute medical fee will soon be over.

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The Greatest Risks of Nuclear Power

To the Editor: Although I found the article by Hendee[1] on risks of medical radiation to be, for the most part, both interesting and enlightening, I believe that Figure 3 and the commentary on it in the text are both misleading and inaccurate. This figure, "adapted from Sinclair,"[2] compares the "actual risk," and the risk as perceived by various social groups (professionals, college students and League of Women Voters) in deaths per year for nuclear power and x-rays, to four other "societal activities" (smoking, motor vehicles, electric power, swimming). Sinclair,[2] however, only lists the rank order of 30 activities as perceived by these groups, and not projected death rates as the figure implies (that is, college students did not project 150,000 deaths per year as the figure shows but did rate nuclear power the most hazardous of 30 "societal activities" that also included swimming, bicycling, mountain climbing, skiing and school football). While Hendee states that nuclear power is the *least* hazardous of the 30 activities listed by Sinclair, Sinclair lists nuclear power 20th, accounting for an estimated 100 deaths per year, four times that of power mowers and school football, five times that of skiing and ten times that of vaccinations, and has no statistics for five of the activities. Hendee does not mention that x-rays were ranked ninth on the list with an estimated 2,300 deaths per year. Hendee does not state how the numbers for the "actual risks" (100 deaths per year per nuclear power) were obtained. While the deaths per year of motor vehicles or school football are probably easily obtainable, the calculation of risk of nuclear power or x-rays must take into account numerous estimates and assumptions. Even if the calculated risks are correct and the danger to an individual person is less for nuclear power than it is for swimming or motor vehicles, the latter are risks the individual may choose not to take.

A recent letter to the editor of the *Annals of Internal Medicine*[3] complained that a paper was misleading because the authors failed to update the references in their literature review (something that is difficult, considering the present lag time between manuscript submission and publication). Hendee's paper does the opposite and fails to "backdate its references." Figure 3 is said to be "adapted from Sinclair." However, Sinclair presents the data in a different form with minimal explanation claiming adaptation from *Decision Research,* but references a paper in *Dun's Review* by Howard and Antilla.[4] Howard and Antilla give unreferenced results of a public opinion poll conducted by a firm called Decision Research on how three groups ranked the risks of various products and activities. They say that the pollsters concluded that people are more willing to accept familiar controllable risks than less familiar, uncontrollable risks. They do not state how the "actual risks," were calculated.

Hence, Hendee's presentation makes light of the risks of nuclear power by making frivolous comparisons of distorted data taken out of context. Isn't it ironic that he complains about "well meaning scientists and political action groups" who distort the risks of radiation exposure? Although I am not personally panicked over the use of nuclear power, as a nonsmoker, nonskier, nonmotorcycler and non-mountain climber, I find the risk of nuclear power greater to me personally. I appreciate that public safety does require some degree of regulation and safeguards for virtually all of the 30 activities listed (such as motor vehicles, handguns, motorcycles, private aviation, commercial aviation, prescription medications and pesticides).

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To the Editor: William Hendee, in "Real and Perceived Risks of Medical Radiation Exposure,"[1] makes the parenthetical point that nuclear power is vastly overrated as a hazard based on his graphic representation of public opinion research previously reported in *Radiology*.[2] A few details of his analysis merit comment.

The fact that Dr Hendee has converted ordinal to cardinal data in order to present the original opinion ranking on the same scale with "actual risks" (deaths per year) is more excusable than is his statement "nuclear power is the least hazardous of all 30 of the activities included in the poll." In actuality, it was listed as number 20 in the source he cited.[2]

Central to his argument is the estimate of 100 "actual" deaths per year for nuclear power.[2] With 75 operating nuclear power plants, this corresponds to a figure of about 1.3 deaths per plant-year of operation, which is within the range of 0.07 to 2 quoted in one study.[3] However, subsumed within this total are 0.07 to 0.3 deaths per reactor-year due to "long-lived isotopes in waste gases, *discounted at 5 percent*" [italics mine]. The need for discounting is explained: "The radioactive gas radon will continue to be produced in uranium mill tailings and uranium mines for tens of thousands of years . . . and will apparently inflict small but continuous health risks on future generations. If

all the predicted deaths over all future years were to be added up, the totals would be very large, 100 to 800 per plant-year."[3] Multiplied by 75 plants, this corresponds with 7,500 to 60,000 deaths per plant-year, moving nuclear power up to between third and sixth place, in the company of motor vehicles and handguns.[2]

The philosophical question of discounting future deaths, "just as future incomes are discounted to represent the smaller value of future events in present-day calculations,"[3] need not be argued here. What is important is that, contrary to popular perception, the greatest risks from nuclear power may accrue in the uranium mining states, where an estimated 140 million tons of uranium mill tailings lie unprotected in both isolated and populated regions.[4]

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Dr Hendee Responds

To the Editor: In my article "Real and Perceived Risks of Medical Radiation Exposure," Figure 3 is a histogram of estimated deaths per year from selected societal activities compared with those from medical x-rays and nuclear power computed by assuming a linear relationship between dose and effect. In all likelihood, this computational procedure overestimates the hazard of x-rays and nuclear power. Superimposed upon the histogram is the perception of relative risk of the activities as revealed by a public opinion poll conducted, as credited in our article, by Decision Research, Inc. The superimposition was provided to illustrate the disparity between real and perceived risks; it was not our intention to imply that the perception of risk is a quantifiable parameter in terms of deaths per year, and this interpretation by Shiffman and Shusterman is a bit surprising.

The argument of freedom of choice in risk assumption is one that has been debated endlessly and to which I have little to contribute other than to suggest that in our society the freedom to choose among risks is probably more limited than we would like to believe. For example, few of us have the luxury to absolve ourselves completely from involvement with motor vehicles.

For reference to the public opinion poll data, Schiffman and Shusterman may wish to follow my example of contacting Decision Research, Inc. of Eugene, Oregon, directly. Dr Shusterman is correct in pointing out that nuclear power occupies the 20th, rather than the 30th, position on the actual risk scale; however, this position is appropriate only insofar as the estimated number of deaths per year from nuclear power has some validity.

In the summary of my paper, the point is made that "multiplying this immeasurably small estimate of risk by very large populations yields numbers that seem to imply that significant health effects occur following exposure to small quantities of radiation." I appreciate the fine illustration of this point furnished by Dr Shusterman.

I do not believe that the accusation of "making frivolous comparisons of distorted data taken out of context" warrants any comment.

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Medical Education

The Oslerian Tradition and Changing Medical Education: A Reappraisal

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Although only 21 of Sir William Osler's 45 years in academic medicine were spent in US medical schools (1884 to 1905), he played a major role in shaping modern medical education in this country. The integration of scholarship with patient care, together with the science and art of medicine, was central to Osler's teaching and writing throughout his career. A classic generalist and a charismatic clinical teacher, he taught by example and was as concerned with the ideals of medicine as with its science and knowledge.

Many changes have reshaped the content, process and concerns of American medical education since Osler's time. Subspecialization and balkanization of medical education and practice have become dominant. Many of the important issues in medicine today do not fit neatly into the domain of any of the established specialties or medical organizations. There is now an urgent need to promote generalist attitudes in medicine, and the Oslerian tradition has much to offer in approaching today's problems in medical education and practice.

Sir William Osler is the prototype of the modern physician who combines the science and art of medicine in a humanistic way.[1] His influence on medicine in this country, as elsewhere in the world, over the past century has been far-reaching by even the most conservative standards. As one measure of his influence, 80 tributes to him were published in various medical journals in 1949, the centennial of his birth,[2] and many hundreds of articles and book materials have been published on his life and work since his death in 1919 at the age of 70.

Osler was born and educated in Canada, receiving his undergraduate medical education in Toronto and Montreal. He then did graduate work in England, Scotland, Germany and Austria, with particular emphasis on physiology and pathology. His career in academic medicine spanned 45 years from 1874 to 1919 and involved four institutions in three countries: McGill University in Montreal (1874 to 1884), University of Pennsylvania (1884 to 1889), Johns Hopkins University (1889 to 1905) and Oxford University (1905 to 1919). The 21 years spent in the United States at Philadelphia and Baltimore have had lasting effects on American medical education, though there is growing concern by some that the Oslerian tradition is weakening amid the many changes in US medical education in recent years.[3]

Because of the importance of Osler's contributions to modern medicine and the extent of current flux and debate in many areas of medical education, it is useful to reassess the prevalence and applicability of the Oslerian tradition in US medical education today.

Osler's Legacy

Osler's contributions cannot be fully understood until one recognizes the deplorable state of medical education that he found in the United States on his arrival in 1884. Throughout much of the 19th century, most American physicians were trained through apprenticeship with a preceptor, as was customary in Europe at that time. Most preceptors were too busy to do much teaching, and a student learned by observation and by reading the few books that the preceptor may have had in his library. During the 19th century a large number of proprietary medical schools were established (there were 90 schools by 1880 and 151 by 1900),[4] many in direct competition with each other. A typical medical school had a faculty of only five or six professors who

Refer to: Geyman JP: The Oslerian tradition and changing medical education: A reappraisal (Medical Education). West J Med 1983 Jun; 138:884-888
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shared the teaching of nine courses—anatomy, botany, chemistry, diseases of women and children, materia medica, obstetrics, physiology, principles and practice of medicine and principles and practice of surgery. Most didactic teaching was by lecture during only four to six months of formal instruction. Few schools had any access to hospitals and many medical graduates had no hospital training. There were few standards and licensing laws were lax. Some states had passed licensing laws, but these merely provided automatic licensing of medical graduates. Many of the proliferating medical schools were little more than diploma mills established by local practicing physicians seeking the prestige of a teaching position and funded by student fees. The weakest medical schools therefore tended to have the largest classes.[5]

The scientific revolution ushered in major changes that required reorganization of US medical schools. For example, advances in bacteriology led to the need for teachers and laboratory facilities in chemistry, bacteriology, physiology and pathology. The inevitable result was a shift of the medical schools to universities, expansion and upgrading of curricula, reduction of class size in many instances and gradual elimination of the small proprietary schools and the apprenticeship method of teaching.[5]

Toward the end of the 19th century, state examining boards began to establish requirements for medical schools, which included an adequate number of faculty, laboratory facilities, hospital experience, three-year and finally four-year graded curricula, required anatomic dissection and admission requirements (high school graduation).[5] On his arrival in Philadelphia, Osler found a leading medical school of its time making these changes. Adapting to this new environment, he steadily gained wide respect as an excellent clinician, a charismatic teacher (particularly at the bedside and in the clinic) and a scholar. He continued his work in both medicine and pathology and published 39 papers on various aspects of clinical medicine during his five years at the University of Pennsylvania.[6]

There is no question that Osler's greatest impact on medical education in the United States came as a result of his years in Baltimore. He was appointed Professor of Medicine at Johns Hopkins University and Physician-in-Chief at the new Johns Hopkins Hospital. Undoubtedly he was attracted by the opportunity to combine patient care, teaching and research at a well-endowed university. He was also attracted by the small classes (18 students in the first class when the new Johns Hopkins Medical School opened in 1893). His priorities in organizing the Department of Medicine there were as follows: the welfare of patients, teaching of medical students and residents and contributing to the advancement of knowledge in internal medicine.[6]

Osler was active in all three of these areas, and his enthusiasm and energy were legendary. He quickly organized his department and faculty to provide patient care and clinical teaching in both the clinics and hospital. By the end of his third year in Baltimore (a year before the arrival of medical students), he had completed the first edition of his *Principles and Practice of Medicine,* which rapidly became the gold standard among medical texts and went through many editions in later years. Of all his achievements, however, Osler regarded his contributions to undergraduate medical education as his most important and personally valued. He at once departed from traditional didactic teaching in favor of small group teaching at the bedside and in the clinics. In his words,

> How can we make the work of the student in the third and fourth year as practical as it is in the first and second? I take it for granted we all feel that it should be. The answer is, take him from the lecture-room, take him from the amphitheatre—put him in the outpatient department—put him on the wards.[7(pp38-39)]

Osler's efforts resulted in the implementation of clinical clerkships for medical students in the clinical years in very much the same form as today.

The integration of scholarship with patient care, together with the science and art of medicine, was central to Osler's teaching and writing throughout his career. His background in pathology reinforced his work as a medical scientist. His descriptions of the natural history of diseases were classic. His distrust of the inappropriate use of proprietary medicines was considered therapeutic nihilism by some—but was clinical wisdom in that most available remedies were ineffective.[8]

Osler upheld the key role of the generalist in medicine: "Have no higher ambition than to become an all-around family doctor, whose business in life is to know disease and to know how to treat it."[7(p51)] He taught by example and was as concerned with the ideals of medicine as with its science and knowledge: "Care more particularly for the individual patient than for the special features of the disease."[7(p93)] Further:

> I have three personal ideals. One, to do the day's work well and not to bother about tomorrow—The second ideal has been to act the Golden Rule, as far as in me lay, toward my professional brethren and toward the patients committed to my care. And the third has been to cultivate such a measure of equanimity as would enable me to bear success with humility, the affection of my friends without pride, and to be ready when the day of sorrow and grief came to meet it with the courage befitting of a man.[7(p84)]

Osler's energies carried him into many related areas. He was a bibliophile and an avid supporter of medical libraries and of journal clubs. He was a strong advocate of professional organizations, especially of the local medical society, and of other medically related organizations for the advancement of medical care and prevention of specific diseases. During his career he published almost 1,200 papers,[9] and was one of the first to recognize the role of bacteria in endocarditis and of syphilis in aneurysms.[10] Despite the breadth of his interests, however, Osler focused on three basic concerns in teaching: (1) you are always a student, (2)

you must treat the person as well as the disease and (3) you must consider the poor beyond all others.[6]

Even in the earliest years at Johns Hopkins, Osler found himself embroiled in the same tensions that are prevalent in medical education today—the running debate and conflict between the generalist and the specialist, between the clinician and researcher. Osler represented the classic generalist clinician-teacher-scholar. Although he recognized the importance of research, he objected to placing a higher value on laboratory over clinical research. His legacy therefore includes the primacy of the patient as person as the object of medical care and medical education, the central role of the clinician-teacher-scholar in medical education and the need for physicians and medical educators to take a broader view of their work and of the relationship of medicine to society. He feared that an overemphasis on specialization in medical education would create a "class of clinicians growing up out of touch, and necessarily out of sympathy with the profession and the public."[11] He was a leader willing to question tradition in medical practice and to eliminate useless procedures. For example, he championed this view about excessive prescribing of drugs:

> Upon us whose work lay in the last quarter of the nineteenth century fell the great struggle with that many-headed monster Polypharmacy—not the true polypharmacy which is the skillful combination of remedies, but the giving of many—the practice of at once discharging a heavily-loaded prescription at every malady, or at every symptom of it.[12]

Osler's many achievements over a full career provide ample evidence for the importance of a generalist voice within medicine and medical education.

The Oslerian Tradition Today

Major changes have reshaped the content, process and concerns of American medical education since Osler's time. The inevitable growth of specialization during the 20th century is clearly the most important single influence on medical education. Between 1930 and today, for example, the proportion of general practitioners and family physicians has totally reversed from about 80 percent to about 20 percent of all physicians in the United States. There are now 23 specialty boards which confer at least 65 general and special certificates. Heavy emphasis since World War II on biomedical research has led to an exponential increase in biomedical knowledge, technology and extensive subspecialization within medical schools. The medical profession has become dominated by specialists practicing and teaching in progressively narrower fields. In a thoughtful paper examining the division of labor in medicine, Menke views the dilemma of specialization in these terms:

> Specialization is both a product of and a contributor to the scientific information explosion in medicine. It subdivides both doctor and patient, increases the difficulty of attaining a clear sense of medical identity for students and young physicians, and places additional strain on the traditional doctor-patient relationship. Specialization . . . contributes to depersonalization, aggravates patient anxieties, and . . . is probably the major factor disturbing traditional ethical and economic patterns in medicine, dominating medical education and research and medical practice, promoting jurisdictional disputes within the profession, and weakening organizational strength and professional power.[13]

The typical medical school today is a very different place from one in Osler's time. Graduate medical education has seen massive growth, and much of the day-to-day clinical teaching of medical students is now carried out by the house staff in most teaching hospitals. In many specialties the research-oriented medical scientist and subspecialist has replaced the clinician-scholar as the predominant faculty role model. The reward system in academic medicine, particularly appointment and promotion criteria, has placed higher value on research and publication than excellence in patient care and teaching. Practicing physicians have been largely excluded from medical teaching in most fields. Patient care on many clinical services is subspecialized and often managed by protocol. It is commonplace, for example, that a well-trained general internist on a full-time faculty has no formal role in the care of his/her patient with acute myocardial infarction in a university hospital in which coronary care is the prerogative of fellows in cardiology and subspecialists in that field.

Two recent observations of current medical education convey different aspects of today's problems. In a paper dealing with medical education and general medical care, McDermott had this to say:

> Our schools have been constantly criticized for emphasizing personal care too little and technology too much. They have entered a consent divorce from the public health field and thus produced fine leaders of medical specialties, but very few of them are equipped to look at the profession as a whole. Above all, medical education has failed badly in teaching ambulatory care.[14]

DeGroot and Siegler[15] criticize the preoccupation of the typical morning report with case review and the gamesmanship of literature recall instead of emphasizing critical inquiry, humaneness of care or even patient outcome. Their concern is that "intellectual inquiry in medical education is being replaced by a narrow view of training designed to produce technicians rather than medical scholars."

Only in the past decade has reemphasis of the generalist role begun to emerge with the development of organized teaching programs in family medicine, general internal medicine and general pediatrics. These fields are beginning to address the larger issues related to medical care and to renew the emphasis of many of Osler's precepts. Their numbers and relative influence in the medical education establishment, however, are still comparatively small. Most departments of medicine, for example, have established divisions of general internal medicine, but full-time faculty in these divisions total only about 400 of the nearly 7,000 full-time faculty in internal medicine in US medical schools.[16] Generalists in all of the primary care fields share similar problems in academic medicine, including heavy clinical and teaching loads, the organizational

and administrative challenges of developing new educational programs and the relative devaluation of their still-somewhat-limited research efforts by those in established specialties.

Where does all of this leave the Oslerian tradition today? Although one can make a good case that some of the *structure* of medical education that Osler helped to shape has survived in a viable way (for example, the undergraduate clinical clerkship), it seems quite apparent that the *process* and even *content* of the Oslerian tradition have become seriously attenuated. The argument can be offered that these changes are the inevitable result of health care and medical education based on highly technologic scientific medicine. The counterargument is that the Oslerian tradition—with its central concerns for both patients and students, emphasis on critical inquiry and clinical problem solving, active participation by clinician-scholar faculty and emphasis on the ideals of medicine—is timeless in its relevance and is at least as important today as it was nearly a century ago.

Some Positive Approaches

In the foregoing discussion I have proposed that the strengths of the Oslerian tradition should be preserved and promoted in medical education, if the public interest is to be served best, by developing the full potential of medicine. If one accepts this view, two further questions remain. One, are there fundamentally new needs in today's world that merit extension of Osler's precepts? Two, what realistic steps can be taken to revitalize the Oslerian tradition in America?

Several major changes stand out as important issues today that were not present in Osler's day:

- The spiraling cost of health care.
- Ethical dilemmas regarding the allocation of resources limited by cost.
- The threat of malpractice liability.
- More active involvement by patients in decisions relating to their own health care.

These changes call for some additions to the content and process of clinical teaching.

Based on the premise that rediscovery and reapplication of the Oslerian tradition are needed, the following constructive approaches are suggested, each of which should be achievable if actively supported by concerned medical educators and clinical teachers. Most of these points are drawn directly from Osler's work and views, whereas others relating to more recent issues represent speculative extensions of his published views in a different time.

- Renewing our commitment to the primacy of patients' welfare, the patient as person and family member and patients' needs as the ultimate reason for both clinical teaching and medical research.
- Shifting the value system and attitudes in academic medicine to reinforce the importance of skilled and humane medical care and excellence in clinical teaching so that they have parity with research productivity.
- Increasing the visibility of the clinician-scholar role model among faculty in clinical departments so that others recognize the central role played by such faculty members in the mission of the department and of the medical school.
- Further developing the generalist role in medicine by supporting the commitment of primary care specialties—that is, family medicine, general internal medicine and general pediatrics—to comprehensiveness and continuity of personal health care.
- Increasing interaction and communication among the primary care specialties and consulting specialties, including sharing responsibilities for the care of complex and life-threatening illnesses.
- Increasing the representation of practicing physicians in clinical teaching as role models of various forms of clinical practice in the "real world."
- Expanding the concerns of clinical teaching to include, in appropriate circumstances, attention to some of the important issues of the day, such as:

    1. Modeling of cost containment without compromising patients' welfare.
    2. Discussion of ethical issues related to cost-benefit and patient outcomes of alternative clinical interventions.
    3. Emphasizing appropriate procedures of informed consent and medical record-keeping.
    4. Encouraging active participation by patients (and family, where indicated) in clinical decision-making based on an adult-adult, physician-patient interaction.

- Extending performance evaluation beyond cognitive factors to include noncognitive aspects of the performance of medical students, residents and faculty, particularly as they relate to interpersonal and communication skills and humaneness of care.
- Broadening the definition of research and scholarship beyond the traditional interpretation of "bench research" to include population-based research, health services research (including quality of care and cost-benefit studies), behavioral research, evaluation of clinical demonstration projects, clinical decision-making research and education research.
- Increasing the integration of research and scholarship related to patient care in clinical teaching settings, whether ambulatory or inpatient, including both the primary care and consulting specialties.

Many of the major issues in medicine today, such as the restructuring of medical practice to better meet the public interest in an era of limited resources, do not fit neatly into the domain of any of the established clinical specialties. Yet the active engagement and leadership by physicians in addressing these problems are vital to their resolution. There is therefore an urgent need for encouraging the generalist approach in

medicine; the Oslerian tradition has much to offer in the process of restoring an appropriate generalist-specialist balance.

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Medical Practice Questions

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

In Vitro Fertilization

QUESTION:

Is in vitro fertilization considered investigational or accepted medical practice?

OPINION:

In the opinion of the Scientific Advisory Panel on Obstetrics and Gynecology, in vitro fertilization can be considered accepted clinical practice under selected circumstances. The complexity of the procedure is such that it should be done only in large centers with rigid laboratory control by physicians expert in the technique. The number of such centers at present is limited.

As the technique and the indications for its use are not yet standardized, in vitro fertilization is not approved for use by all practitioners. Because advances in the field of in vitro fertilization are rapid, this question merits review in the near future.

Medicine in Perspective

Ethical Crises and Cultural Differences

AFAF IBRAHIM MELEIS, PhD, *and* ALBERT R. JONSEN, PhD, *San Francisco*

Generalizations about patients without careful attention to their cultural background, their values and norms could lead to a number of ethical crises. The informed consent, disclosure of diagnosis and prognosis, and discussions of termination of treatment are reflections of Western cultural values. They represent respect for autonomy of clients and respect for openness in communications. For patients from other cultures such practices have different meanings that may violate their own values. The result of such conflict in practices and meanings can render the relationship between patients and health care personnel difficult at best and distrustful at worst.

Contemporary medical ethics strongly endorse certain practices such as informed consent, disclosure of diagnosis and prognosis, and termination of treatment under certain conditions of terminal illness. These practices are endorsed, in part, because they reflect certain values widely held in Western culture: the autonomy of the individual person, the imperatives favoring truthfulness and open communication, and the realistic assessment of the efficacy of medical care.[1] However, American physicians who accept these practices and the values they represent may encounter patients from cultural backgrounds where the practices are not meaningful. Physicians, acting in good conscience, may find themselves in difficult situations when such patients and their families react negatively or paradoxically to these practices. An example of such a difficult situation is reported and the case analyzed in light of the cultural expectations of the patients.

The patient presented in this case is an Arab, coming from a culture whose representatives, though not seen as frequently in American medical care as Hispanics and Asians, are appearing more and more frequently. Although the cultural values described in this article are proper to Arabs, the lesson is universal: it is necessary, from both an ethical and a practical viewpoint, to comprehend the values and beliefs of patients from cultures quite different from our own.

Report of a Case

Mr Ahmed, a 28-year-old man of Egyptian birth, had come to the United States six months earlier to join his mother, two brothers and one sister. He came to the emergency room of a university hospital with a severely swollen and inflamed neck. He was cachectic and dyspneic. Swollen, rubbery lymph nodes were noted in the neck. He spoke English haltingly, but did communicate with his brother's help that he had been told several years earlier that he had cancer. He was treated in several foreign hospitals, but had not seen a doctor since his arrival in the United States. A presumptive diagnosis of Hodgkin's disease was made, and he was admitted for treatment of cellulitis and edema of the neck as well as for evaluation for chemotherapy. His family accompanied him and remained around the clock in the visitors' room. The mother spoke no English; the brothers and the sister spoke it adequately but not fluently.

Informed Consent

Mr Ahmed's medical history was not well documented. When he and his family were questioned about personal or family health history and business or social status, they reacted with suspicion. Providers of care did not make any effort to clarify the relationship between the "intrusive" questions and the medical problem. In some cultures, the fewer the number of questions asked, the less intrusive they are and therefore the better the health care.[2] This is one of the values that Arab-Americans hold and is certainly not a value of the Western health care system. As a result, many questions went unanswered.

Mr Ahmed had been treated in hospitals in Greece and in England before coming to the United States. Clinical examination showed signs consistent with

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Hodgkin's disease, but there was no reliable information about the stage of the disease. Mr Ahmed had said he had been sick for about three years and that he had been treated with x-rays and with drugs. Node and liver biopsy studies seemed appropriate and were recommended to him. The family seemed to agree verbally with the recommendations. However, when the resident asked Mr Ahmed to sign the consent form, he refused. His mother and two brothers, who were in the room at the time, strongly supported him and seemed very angry. The resident could not understand the reason for the refusal. Mr Ahmed simply refused to explain, and the language differences presented a barrier to clearer communication.

Discussion

Anglo-American law has long required consent for surgical procedures. Except in emergencies, a doctor who operates without the consent of the patient can be charged with battery. In recent years, the doctrine of consent has been elaborated into a doctrine of *informed* consent: the physician must inform the patient of the nature of the illness, of the benefits and risks of treatment, and of alternatives. The patient may assess this information and accept or refuse the doctor's recommendations. The ethical basis for the doctrine of informed consent is respect for the autonomy of the patient—that is, acknowledgment by the doctor (and all others) that the patient is a person with the right to control his or her own life. The value of autonomy has deep roots in Western culture and has been an important concept in Western philosophy. In addition, autonomy has been associated with the ability to make a rational decision based upon knowledge and with the opportunity to choose among several options. Thus, even though the legal and ethical doctrine of informed consent has only recently become prominent in medical practice, it has a firm place in the Western value system.[3-5]

It has become common to request consent and, for many procedures, to ask the patient to sign a consent form. Consent in writing has a different symbolic meaning to an Arab in his homeland, and such meaning becomes more complex when an Arab interacts with foreign (to him) health care workers. Once Arabs give their verbal agreement to a contract, they consider it binding and equal to their written agreement. To press them further to a written agreement only suggests mistrust of their verbal contract. The legal validity of such verbal contract is not the essential issue; personal honor is at stake and is challenged when someone is pressed to give a written consent after a verbal consent is already given. Therefore, this point causes many frustrations to health care professionals when they ask or demand a written consent for every procedure carried out on patients, although it is a plausible explanation for the seeming paradox on the part of an Arab patient toward verbal versus written consent.

Even the *request* for consent creates a problem. Arab-Americans have respect for authority figures. Such figures represent expertise based on experience and education. This means speaking knowingly about the matter at hand, and it also means making decisions for others and being accountable for such decisions. Therefore, the concept of options, alternatives and taking responsibility for one's actions that is unique to the Western hemisphere is foreign to Arab-American patients. For an Arab-American, taking responsibility for one's decisions is not accomplished through a mere signature on a consent form; it can only be accomplished when a person has acquired the education and experience that allows him to make informed decisions and give an informed consent.

It is not only the issue of informed written consent that is a problem for Arab-American patients, but also the manner in which such consent is requested. Arabs tend to want to chat around a theme and to take their time before the crux of the interaction is approached.[6] They are not too eager to get down to business and prefer to get to know each other personally and about each other's family before the business transaction is handled. The informed consent process is professional, technical and succinct; it appears highly inhuman to the Arab eye. This becomes even more complicated when a patient's condition is critical. Not only do the patient and the family expect to receive humanistic care, they expect all those who surround them to be emotional and subjective. The last thing they would expect is a cold, calculated transaction. Health care professionals who ask for written consent during crises are perceived as cold and calculating, and therefore are to be mistrusted. On the other hand, health care professionals will label such patients as uncooperative and noncompliant, and they readily consider them "difficult patients."

The perception of the efficient but mechanical professional attitude is most certainly not confined to the Arab-American patient's way of thinking. Patients from other cultures, such as Latinos, have expressed similar views.[7]

Disclosure of Information

On the second hospital day, Mr Ahmed was sipping soup and choked. As a result of difficulty in placing the tracheotomy tube, he suffered five to seven minutes of anoxia. Use of a respirator was begun and the patient remained in deep coma, although his neurological status did not meet brain death criteria.[8] After Mr Ahmed had aspirated and the neurology consultants had confirmed anoxic encephalopathy with poor prognosis for recovery, the family was approached by the resident and an intern who spoke some Arabic. They explained the situation as fully and as frankly as they could under the circumstances of limited communication. The interview was disrupted by extreme manifestations of grief by the mother and by the family's attention to her rather than to the doctors. However, the physicians felt they had communicated the essential information: Mr Ahmed had suffered serious brain damage and would, in all probability, not recover con-

sciousness although he might continue to live, with or without respiratory support. They did not feel they could bring up the issue of termination of life support under the circumstances. However, in subsequent days they did so and were met with anger and outrage.

In Western culture, direct and honest communication of facts about a situation is highly valued. Deceit is considered reprehensible, and circuitous as well as metaphorical modes of communication are not encouraged. Within this general approbation for direct communication, there has long been a debate among physicians about how frankly fateful information should be imparted to patients. In recent years, commentators on this issue have come to favor full and truthful disclosure. They argue that not only is the truth demanded by ethical principle, but there is no evidence patients are harmed by it and considerable experience indicates that they are helped by knowing their diagnosis. Thus the physicians in this case acted in accord with values that are widely supported by their culture and, in recent years, by the profession.

Arabs, while valuing open communication and truth, view differently the circumstances involving crises, disaster and, most particularly, those related to terminal illness and impending death. Other cultures hold such values as well.[2] To confront a patient with his grave diagnosis and poor prognosis is not only a tactless act but an unforgivable one, one which in fact might bring disaster to that person. Such a confrontation is not congruent with the rules that govern communication of Arab Moslems. Hope helps a patient mobilize his own resources to cope with the illness, even if such hope is false by Western standards. As long as the patient has faith in Allah and his power, hope is never false. To utter the words related to the grave situation in front of the patient or his closest kin—especially if the kin is female—as we invariably do in the West because of our belief that patients are entitled to the truth, only renders the patient hopeless and ready to give up. Worse yet, to do so suggests that the health professional has given up on the patient and therefore will not continue to handle the case with the same care and expertise as before.

Members of the family are expected to act as a clearinghouse of information, especially information related to grave diagnoses.[9] Health care professionals should couch the truth with unfailing hope and protect the patient by communicating the truth to other persons in the family who have been identified as spokespersons, ones who are looked up to by family members as the advisors and counselors (men before women and older before younger).

This refusal to hear the truth might be considered by Western interpreters to be denial. The Eastern mind has a different interpretation. Only God knows how poor a prognosis is; only God knows whether we should give up or not. Our hope should never wane or else God's help will not be forthcoming. How could the patient's family trust health professionals who have declared a "no hope," a "hands off" or a "wait for death" policy? Arabs, whether Christian or Moslem, value hope until the bitter end. Hope is only shattered when the physician—representing the power of Western medicine—declares the prognosis of impending death. This declaration can engender deep mistrust for the physician, and this mistrust is conditioned by social values, religion and the reverence accorded Western medicine.

Arab-Americans value Western medicine highly. Western medicine epitomizes expertise, science and technology. Patients who die in the Arab world die because it is the will of Allah, but also because of the inadequacy of equipment, medications and the like. Even though Arab-Americans continue to speak of the *evil eye* and of hot and cold as contributing to disease, Western medicine is sought and practiced assiduously. It is believed that more intrusive procedures are more effective: intramuscular injections are preferred to pills, and intravenous treatment to intramuscular.[10] In spite of this respect for medicine, however, medical preparation for impending events such as birth and death is diametrically opposed to an Arab's values and beliefs. These should be left in the hands of God until they actually occur. To do otherwise is to outguess God and could bring eventual disaster to the family.

An Arab's extreme reluctance to speak of death, to anticipate and prepare for it, should not be confused with his acceptance of its inevitability. An Arab does not deny the reality of death,[9] but Arabic beliefs forbid speaking of it or, worse yet, expecting it at a specific time proclaimed by another mortal. If, as it sometimes happens, it is necessary to speak of death,

> two phenomena occur; God is mentioned in one form or another, and a euphemism is substituted for the word "death." Often the term used is an ingenious condensation of the two. For example, the dead person is spoken of as "One Whom God has Claimed as a Debt" (Mutawaffi), as "One Forgiven" (Marhoom), or as "One Who Passed to God's Mercy" (Maghfour Lahu); or he is referred to as the one "Lost" (Al-Faqeed), or the "Precious Lost" (Al-Faqeed Al-Ghali), after which God's forgiveness is invoked by a second phrase.[11]

Under the very unique circumstances when death has to be spoken of in futuristic terms, it is never connected with a particular person and, even then, it has its euphemisms, such as "Al-Maktoob" or "Al-Muggadder" ("what is willed" or the "Destined"), then evil is quickly denounced by saying "Baad-Al-Shar."

This cultural background rendered Mr Ahmed's family suspicious and distrustful of the intentions of the health care personnel. Matters became worse when the question of termination of life support was introduced.

Termination of Life Support

The attending physician and the house officers reached the conclusion that Mr Ahmed had suffered irreversible brain damage. In addition, they suspected he was also suffering from a lethal disease in an advanced stage. It was their unanimous opinion that respiratory support should be terminated. Although Mr Ahmed was not "brain dead" because he still had brain stem functions, the physicians believed his recovery to

"conscious and sapient life" was beyond the realm of possibility. They consulted with the medical ethics committee of the hospital and with legal counsel and were supported in their opinion that termination of life support was ethical and in accord with leading legal opinion. Thus, they decided to recommend this to Mr Ahmed's family. They were also aware they did not need the family's permission to act on their medical decision, but they did wish to have the family's understanding and agreement.

In following this course, the physicians were acting in conformity with a growing consensus of medical, legal and ethical opinion. The technology of critical care medicine is not only capable of supporting seriously ill patients during crucial episodes, it is also able to support organic function when little or no therapeutic potential remains. The limitation of such support to those situations where some benefits are still possible or probable is broadly, if not unanimously, approved by physicians and the general population. "Being kept alive as a vegetable" is not, for most persons, a desirable goal.

Within this general consensus, many debates have taken place about what is permitted and what is forbidden. An extensive literature about termination of medical intervention, about active and passive euthanasia, about "order not to resuscitate" has appeared.[12] Fifteen states have passed "brain death" legislation that permits physicians to terminate life support when evidence supports the diagnosis of total and irreversible cessation of brain function, including the brain stem.[8] Ten states have passed legislation giving legal status to those documents, sometimes called "living wills," in which persons in good health can direct their physicians to cease supporting interventions when hope of recovery is lost.[13,14] A number of important legal opinions, starting with the Karen Ann Quinlan case, have addressed the problem. While these differ in many respects, they move in the direction of giving legal sanction to discontinuing life support, or not initiating medical intervention, when attainment of significant medical goals appears unlikely.[15]

The health care personnel had already violated the values and beliefs of Mr Ahmed's family on several accounts. Many questions were asked about such personal things as the patient's and the family's health and social status, questions which were regarded suspiciously because the nature of the relationship between the medical problem and the personal questions was not apparent. A grave prognosis was announced, even before the choking incident, and Western medicine failed in taking care of the consequence of the choking. The last straw for the family, who were deeply religious and who espoused an Arab value and belief system, was to be confronted by questions related to "termination of life support," a discussion that managed to heighten suspicion and mistrust and that prompted the family to take turns around the clock watching their beloved member to halt any attempts on the health care personnel's part to terminate life support.

Mr Amed's two brothers and sister took leaves of absence from their jobs to be with the patient and their mother, who was a constant vocal and angry companion. They raised many questions and made the staff very uncomfortable. The family's behavior, explained within the trust/nontrust context, has even more meaning when examined in relation to a culture's methods of coping with stress.

Coping Styles of Arabs

There are several predominant styles of coping with stressful events: problem solving, information seeking, direct action, inhibition of action and intrapsychic process.[16,17] A person uses one or more, depending on his or her appraisal of the stressful event as a threat or a challenge.[18]

An Arab's predominant coping style is "turning to others" for help and advice.[19] In doing so, the need for others' help is not directly communicated; rather, it is understood and acted upon without being verbally articulated. The expected help must be offered with persistence and force and, whether the seeker acknowledges the need or not, the offer must be repeated. This creates one of the major issues encountered in caring for Arab clients. Their beds are invariably surrounded by relatives and friends. The health care providers are amazed at the number of persons who are constantly in the way of the hospital routine and who seem to interfere with the kind of care the health care personnel prefer to give.

Such behavior has a different meaning within the Arab cultural context. Arabs have very high affiliation needs even when not in crisis or under stress. This is manifested in their social patterns and preference for occupations that involve constant human interaction and contact. When under stress of illness, such needs are intensified; the patients must be constantly bathed in care and attention, and the extended and nuclear families and friends must become exorbitant in manifesting such care. To show their concern for the patient, family members and friends are expected to manifest two sets of behavior. They must be around the patient as much of the time as possible, and they must become very demanding of health care personnel. Such demanding demeanor portrays caring for the patient as well as respect for the health care system's omnipotence in "curing" and handling the client's problems. It is a manifestation of total resignation to simply leave the matter to God and not to question the health care system. Such behavior is misinterpreted by health care professionals and leads them to reject and avoid Arab patients.

In this case, health care providers attempted to improve the situation by doing what might appear, to Western eyes, quite an appropriate thing: they called in a religious advisor. A Moslem sheikh was summoned to comfort the family. The very sight of the sheikh in the hospital room of the comatose patient heightened the family's and friends' mistrust of the professionals caring for the patient. To them, the well-meaning inten-

tion of the medical personnel was symbolically analogous to bringing in a Catholic priest to perform the last rites and to comfort the family.

As discussed above, an Arab Moslem family (or an Arab Christian family, for that matter) is not expected to plan for death, or to ever give up hope, even under the gravest of circumstances. To do either is bound to defy God's will and might bring about a worse prognosis at best and a premature death at worst. The sheikh's appearance, therefore, contradicted their belief. One might ask, "Why did a Moslem sheikh agree to the mission?" The Moslem sheikh was a non-Arab; therefore it is possible that there were conflicting cultural values that prompted such a response. Possibly he believed the request had been made by a more Westernized Arab-American Moslem. To be called to help and to respond by questioning the wisdom of such help is not congruent with the Islamic laws guiding a Moslem sheikh.

The damage from this well-intended act was profound. The family of the dying, comatose patient perceived it as a sign of hopelessness on the part of the health care team. They became extremely fearful that, in spite of their pleas and their hope, the beloved patient would now be willfully left to die and no measures would be taken to save him, all of which was against their wishes. Suspicion increased; cooperation decreased.

Conclusion

Generalizations about any culture or people must be viewed critically. Within broad cultural communities there are almost infinite differences; persons from any culture are not stereotypes but unique. Still, whether Arab patients are Saudis, Kuwaitis or Egyptians, whether they are city or country reared and whether they are Christians or Moslems, there is a core of Arabism. Their cultural perspective can encounter profound difficulties when it meets the values of the Western system of health care. There are differences in values, in perceptions, in expectations, and in style of expression and behavior. This article has described some of these that go beyond mere difficulties in linguistic communication; they touch the most serious ethical responsibilities of health care providers, as we perceive these responsibilities. The experience described above involved the obligation of obtaining permission to treat and deciding to terminate treatment. The performance of these responsibilities was rendered extremely difficult by the inability on both sides to understand how actions and statements were perceived within the cultural context.

There are no simple solutions to this problem. It occurs whenever persons from a culture different from the Western one, in which most of our professionals have been raised, enter the health care system in any number. Professionals cannot, of course, become instant anthropologists. They cannot master the nuances of behavior formed by a very different type of education and rearing. They may be able, with effort, to read a bit about their clients' mores and psychology; they may be able to learn a bit of their language. They can, more often, call for help in interpreting behavior. This is perhaps the most frequent failure of Western professionals. They have supreme confidence in their ability to manage a difficult situation. They rarely consider seeking consultants, who may not be medical professionals, to help them assess and solve difficulties in language, in life-style and in value preferences. However, institutions that serve patients from different cultures have an obligation to identify persons who can provide such help. They should be invited to educate the staff and should be called upon for consultation. For example, though the situation described in this case would be a difficult one to handle, no matter which culture a person belonged to, if the health care personnel had been aware of the cultural mores of the Arab family they could have prevented several major issues described in this discussion. More significantly, they would have avoided the mistrust that evolved from direct disclosure of a grave prognosis and from misinterpretation of the meaning of the consent procedures. They could have cast the numerous personal questions with a meaning related to benefits to the patient rather than to the hospital, as is often perceived by patients.

Finally, health care professionals should be sensitive to and care about the deeply felt values of their patients. These values may appear absurd or irrational to the Western eye, particularly eyes that see the world in scientific and technical images. Yet if we have learned anything from sociology and anthropology, it is that the values and behaviors of all cultures, viewed with understanding and sympathy, have profound meaning for survival and human well-being.

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Commentary

Commentary From Coeur d'Alene: One Baby—Or Two?

E. R. W. FOX, MD, *Coeur d'Alene, Idaho*

No one will deny that Jimmy Carter possesses a keen social consciousness. As President he charged a consortium of government agencies with the responsibility of making a prognosis of what our nation and our world would be like in the year 2000.

This effort resulted in the production of three heavy volumes, titled *The Global 2000 Report.*[1] Within these tomes lie dire predictions of a burgeoning world population, a depletion of natural resources and an ever-increasing price we will pay for the privilege of living on this planet.

Nowhere in these weighty volumes are we given a quick and easy solution for these cosmic problems. Conservation, of course. Population control, yes. That goes without saying.

It is unlikely that the global report of Jimmy Carter's will do much to change the course of events, at least not in the United States of America. Affluent America hesitates to change its ways of living. We enjoy the luxuries of life. We cherish our individualism and we will challenge the right of anyone to change our life-style, or to limit the size of our families. We have blind faith in the belief that tomorrow will bring us more bounteous chunks of gracious living, ours to enjoy into eternity.

Even though we are reluctant to accept the pessimistic forecast of the demographers, we should at least be willing to consider the probabilities.

Let us assume, as one probability, that in the year 2000 our fields have become less fertile, our streams are flowing at a low level and the cost of raising a family is soaring to an all-time high. What would be the logical course to follow? Obviously, we would opt for population control through the limitation of family size.

How, then, would that be accomplished? Will this be achieved through a voluntary effort of the American people or must there be government control? A look at how the "backward" nations of our world are enforcing population control might be instructive.

The People's Republic of China has just announced the results of its census—accomplished, incidentally, with the aid of American computer technology. There are now 1.38 billion mouths to be fed in this land of low productivity. The Chinese leaders know that even if they succeed in holding to a 1 percent population increase, there will still be 1 million Chinese babies born every month.

Their solution is direct, aimed at the Chinese workers' already very slim pocketbooks. When a couple marries they are visited by a government representative. They are told, "The good of the great nation of China lies in the careful limitation of family size." Then the rules are spelled out. During the first pregnancy all care will be free, and the mother will be given generous time off from work with full pay. If a second pregnancy occurs, abortion is urged. Should the couple choose to go through with this pregnancy, the reimbursement for maternity care is cut to the minimum, and there is no paid-for postpartum vacation. If, by chance, the couple is so thoughtless as to allow a third pregnancy to occur, the full weight of family and community pressures is brought to bear. There must be an abortion with a permanent sterilization to follow.

This approach can be successful in a communist country where the government controls the pursestrings and writes the paychecks.

In the Philippines, on the other hand, the efforts have been directed toward a positive program of conception control. The implementation of this program initiated by President Marcos rests in the hands of a nonphysician, paraprofessional person who, in his assigned district, carefully oversees conception control. This person, who makes his rounds on burro or motorbike, is given the impressive name of Barangay Supply Point Officer (BSPO).

The BSPO works as a government agent, maintaining strict discipline, while dispensing advice and contraceptives. Such careful surveillance may include a visit to homes, where the BSPO does not hesitate to investigate the most intimate details of family life: "Is Serena taking her birth control pills regularly? Does Jose understand the proper use of the condom, or is he perhaps ready for permanent sterilization?" This one-on-

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one paternalistic population control program has effectively lowered the birth rate in the Philippines.

Thailand is another poverty stricken, overpopulated country whose national leaders have recognized the need for limitation of family size. In the years past the average number of infants born to a Thai mother was six. A vigorous family planning program has, in the past decade, reduced this number to three. A further reduction in maternal fertility to two or less is the goal of family planners.[2]

This exemplary success has been accomplished largely through education. The planners recognize that fertility and educational levels are inversely related. As a result of the educational programs the Mother Hubbard level of reproductive information has been replaced by basic knowledge of how and why pregnancy occurs and what can be done about prevention.

To attain these improved educational levels the government launched a three-pronged program:

1. *Education of school children.* Because the average duration of schooling in Thailand is six years, family-life education had to be introduced promptly, presenting a more specific type of information American educators still shy away from.

2. *Family planning.* In each village or district (tambon) there are family planning clinics, most of them supervised by nonphysicians. These clinics are an integral part of the national health service system and supply not only sex education and counseling, but birth control pills and devices.

3. *Postabortal and postpartum conception control.* Abortions (most commonly induced by massage!) are free at the national health clinics. Elective terminations and term deliveries are usually performed by nonphysicians—midwives and "barefoot doctors." This is considered the opportune time to give the parturients strong directives, either in the form of contraception or permanent sterilization.[3]

Such data from "backward" countries are interesting, but most of us living in this land of plenty fail to see how it has any bearing on our situation here in the USA, either now or in the year 2000. We are satisfied with the status quo.

It may just be that in our apathy we are blind to the increasingly important role being played by nonphysicians in the area of population control in our own country, or that here in our own hometowns governmental and quasi-governmental agencies are concerning themselves with fertility control.

Our public health service provides pregnancy tests and the care of pregnant teenage girls. The "free" women's clinics hand out birth-control pills and condoms, and make abortion referrals. Psychologists and social workers take part in family planning for the members of their "caseloads." And they do it well.

Ms Lee Minto, Executive Director of Planned Parenthood, Seattle/King County, reports that during 1980 in the state of Washington 30,000 abortions were carried out, and of those almost a third were done on unmarried teenagers between the ages of 15 and 19.[4] Planned Parenthood is convinced that counseling of these women can in some degree prevent the unhappiness of these unwanted pregnancies.

Population control, fertility control, is with us even though we may not recognize it as such. Our younger generation is being conditioned to accept the concept of family planning under the watchful eye of government agencies. These population control programs are, of necessity, carried out by nonphysicians. These persons are not BSPO's, they do not ride burros or motorbikes. But it is at least conceivable that by the year 2000, when the *Global Report*'s predictions would come true, we, too, will see further invasion of our privacy, further intrusion into our family lives.

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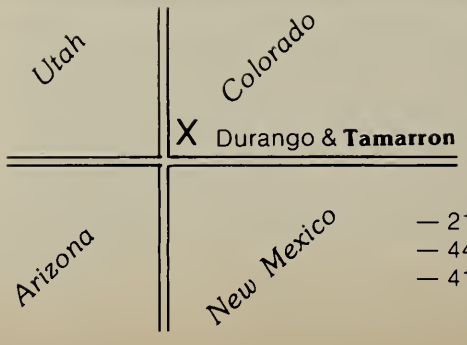

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In Memoriam

California Medical Association

CARLSON, EVERETT, San Francisco. Died February 4, 1983, in San Francisco, aged 86. Graduate of the Stanford University School of Medicine, Palo Alto-San Francisco, 1924. Licensed in California in 1924. Dr Carlson was a retired member of the San Francisco Medical Society.

LANDES, JOHN S., San Jose. Died January 13, 1983, aged 66. Graduate of Western Reserve University School of Medicine, Cleveland, 1942. Licensed in California in 1951. Dr Landes was a member of the Santa Clara County Medical Society.

MANNERSTEDT, GORDON O., Sacramento. Died January 17, 1983, aged 78. Graduate of University of California Medical School, Berkeley-San Francisco, 1933. Licensed in California in 1933. Dr Mannerstedt was a retired member of the Sacramento-El Dorado Medical Society.

MCKINNON, ANGUS, Placerville. Died January 26, 1983, aged 82. Graduate of University of Minnesota Medical School, Minneapolis, 1925. Licensed in California in 1925. Dr McKinnon was a member of the Sacramento-El Dorado Medical Society.

MCMULLIN, JOHN F., Riverside. Died January 27, 1983, aged 73. Graduate of Jefferson Medical College of Thomas Jefferson University, Philadelphia, 1934. Licensed in California in 1947. Dr McMullin was a retired member of the Riverside County Medical Association.

MCPHEE, VICTOR C., San Francisco. Died January 27, 1983, in Daly City, aged 84. Graduate of St. Louis University School of Medicine, 1925. Licensed in California in 1925. Dr McPhee was a retired member of the San Francisco Medical Society.

OVERSTREET, EDMUND WILLIAM, San Francisco. Died January 21, 1983, in La Jolla of cancer, aged 74. Graduate of Johns Hopkins University School of Medicine, Baltimore, 1935. Licensed in California in 1939. Dr Overstreet was a retired member of the San Francisco Medical Society.

RACZ, DESIDER, Santa Rosa. Died January 11, 1983, in Santa Rosa of heart disease, aged 80. Graduate of University of Dubrecen Fakulty of Medicine, Hungary, 1934. Licensed in California in 1951. Dr Racz was a member of the Sonoma County Medical Society.

New Mexico Medical Society

BERGENER, KARL L., Roswell. Died September 27, 1982, in Roswell, aged 71. Graduate of the State University of Iowa College of Medicine, Iowa City, 1937. Licensed in New Mexico in 1954. Dr Bergener was a member of the Chaves County Medical Society.

CURRAN, WILLIAM S., Albuquerque. Died April 11, 1983, in Albuquerque, aged 57. Graduate of Harvard Medical School, Boston, 1952. Licensed in New Mexico in 1963. Dr Curran was a retired member of the Albuquerque and Bernalillo County Medical Association.

GAARDE, FREDERIC WILLIAM, JR, Santa Fe. Died September 24, 1982, in Santa Fe, aged 66. Graduate of the University of Minnesota Medical School, Minneapolis, 1943. Licensed in New Mexico in 1971. Dr Gaarde was a member of the Santa Fe County Medical Society.

JACOBSON, ALAN, Albuquerque. Died March 28, 1983, in Albuquerque, aged 70. Graduate of the University of Maryland School of Medicine, Baltimore, 1937. Licensed in New Mexico in 1947. Dr Jacobson was a retired member of the Albuquerque and Bernalillo County Medical Association.

TRACY, MARY J. WESTCOTT, Santa Fe. Died December 17, 1982, aged 65. Graduate of the University of Illinois College of Medicine, Chicago, 1951. Licensed in New Mexico in 1974. Dr Tracy was a member of the Santa Fe County Medical Society.

Utah State Medical Association

BODNAR, MODEST, Salt Lake City. Died March 30, 1983, in Salt Lake City, aged 45. Graduate of University of Rochester School of Medicine, Rochester, NY, 1967. Licensed in Utah in 1970. Dr Bodnar was a member of the Salt Lake County Medical Society.

DALRYMPLE, ROBERT MERRITT, Salt Lake City. Died April 17, 1983, in Salt Lake City, aged 65. Graduate of Cornell University Medical College, New York, 1943. Licensed in Utah in 1948. Dr Dalrymple was a member of the Salt Lake County Medical Society.

GRAFF, ARNOLD LA MAR, JR., Cedar City, Utah. Died February 22, 1983, in Cedar City, aged 49. Graduate of the University of Utah College of Medicine. Licensed in Utah in 1959. Dr Graff was a member of the Iron County Medical Society.

LEARNED, LELAND O., Salt Lake City. Died March 23, 1983, in St. John, Virgin Islands, aged 63. Graduate of Northwestern University Medical School, Chicago, 1943. Licensed in Utah in 1943. Dr Learned was a member of the Salt Lake County Medical Society.

NEWMAN, WILLIAM REECE ELTON, Salt Lake City. Died April 8, 1983, in Salt Lake City, aged 74. Graduate of University of Nebraska College of Medicine, Omaha, 1946. Licensed in Utah in 1953. Dr Newman was a member of the Salt Lake County Medical Society.

PACE, WILLIAM D., Salt Lake City. Died April 8, 1983, in St. George, aged 70. Graduate of Temple University School of Medicine, Philadelphia, 1940. Licensed in Utah in 1941. Dr Pace was a member of the Salt Lake County Medical Society.

Book Reviews

The Western Journal of Medicine *does not review all books sent by publishers, although information about new books received is printed elsewhere in the journal as space permits. Prices quoted are those given by the publishers.*

RECENT DEVELOPMENTS IN CARDIOVASCULAR DRUGS—Edited by John Coltart, MD, MRCP, FACC, Consultant Physician in Cardiology, St. Thomas' Hospital, London, and David E. Jewitt, BSc, MB, BS, FRCP, Director of Cardiac Department and Consultant Cardiologist, King's College Hospital, London. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1982. 348 pages, $59.00.

This book is the result of a symposium which was held on the topic of cardiovascular drugs. The volume, therefore, is a mixture of the strengths and weaknesses of a symposium turned into a book.

On the negative side, there is uneven treatment of the various topics, presumably due to the time each author spent in providing a written record of his talk. Some very important topics are only briefly covered, while other topics occupy lengthy chapters. There is also a highly selective list of topics and drugs. Thus, this volume is but a sampling of some new developments which were felt to be of importance when the symposium was organized.

On the positive side, the information is relatively new and does deal with a number of drugs that are not yet available for clinical use, especially inotropic and antiarrhythmic drugs. The discussion at the end of each chapter also provides differing points of view, which is always one of the most valuable aspects of any symposium. Some of the general chapters are particularly well done, so that one can certainly benefit from reading this volume. In general, it stands on its own as a good example of the kind of report that can be prepared from an interesting symposium on up-to-date cardiovascular therapy.

WILLIAM W. PARMLEY, MD
Professor of Medicine
University of California
San Francisco

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GUIDE TO DIAGNOSTIC IMAGING—Volume I: THE LIVER & SPLEEN—Alexander Kovac, MD, Chief, Radiology Service, Veterans Administration Medical Center, Phoenix; Adjunct Assistant Professor of Radiology, University of Arizona College of Medicine, Tucson. Medical Examination Publishing Co., Inc., 3003 New Hyde Park Road, New Hyde Park, New York 11040, 1982. 229 pages, $33.00 (hardcover).

This is the first volume in a series that is intended to provide guidelines for ordering imaging examinations for those who are "either closely or remotely associated with medical imaging." The task that the author has set for himself in this series is an important one, but also a very difficult one. This first volume on the liver and spleen includes chapters or sections on anatomy, embryology, physiology and laboratory tests as well as the various imaging modalities and disease categories. Although the overall presentation provides useful information to the uninitiated, I think that the imaging subsepecialist in each of the areas of computed tomography, ultrasound, nuclear medicine and angiography will take exception to many of the details in the discussion of his imaging modality. Tables are provided throughout the book with comment on the usefulness of the various imaging modalities. However, the comments are not sufficiently specific to allow the nonimager to determine the appropriate diagnostic imaging algorithm for a given clinical situation. In addition, it is disconcerting to find no mention of the desirability for consultation between the referring physician and the radiologist. Such consultation is particularly important at a time when rapid evolution of imaging modalities is occurring and when local expertise and equipment in the various modalities varies significantly. The strength of this book is its overview of general information related to the liver and spleen. This information may be most useful to imaging technologists and others who are involved in carrying out diagnostic imaging studies, but will probably be of limited use to those who are responsible for ordering imaging procedures.

WILLIAM C. KLINGENSMITH III, MD
Associate Professor of Radiology
Director, Division of Nuclear Medicine
University of Colorado Health Sciences Center
Denver

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THE YOUNGEST SCIENCE, NOTES OF A MEDICINE-WATCHER—Lewis Thomas, MD, chancellor of the Memorial Sloan-Kettering Cancer Center, New York. Viking Press, Inc., 625 Madison Ave., New York, NY 10022, 1983. 270 pages, $14.75.

In this, the meditations of a modern man of medicine, we sit at the feet of a warmhearted storyteller. Dr Lewis Thomas is a medical philosopher with a keen sense of history. He is a talented essayist. In this book he speaks lovingly of the early days when his father practiced the *art* of medicine. As his story progresses he seems to stand back in order to observe, with awe, and some discomfiture, as *art* gave way to science. This, in spite of the fact that as a research worker he has taken part in this metamorphosis.

Dr Thomas writes with honesty and with respect for intellectual curiosity. His essays reach into nooks and crannies of the wonderful world of medicine. He makes the story of biochemistry, DNA-RNA and miracle medications understandable. He views with abject wonder the "computerized devices that reveal electronic intimacies of the flawed heart or malfunctioning brain with a precision far beyond the touch or reach, or even the imagining of the physician at the bedside a few generations back."

Do we discern, as we read between the lines, that this practitioner of the science of medicine yearns for a return to the art of medicine? He regrets that "too many doctors are more committed to the machinery than to the patient." He fears that technology has increased the distance between the physician and patient.

This is an honest, down-to-earth evaluation of medical practice in 1983. It will be of interest to young people entering the world of medicine. Indeed, it may give them pause. He writes, "If I were a medical student or an intern just getting ready to begin, I would be apprehensive that my real job, caring for sick people, might soon be taken away, leaving me with the quite different occupation of looking after the machines."

On the other hand, the practicing physician who proudly wears several service stripes on his white uniform, will enjoy waves of nostalgia as he reads this elegant book. And then, as he writes his orders for CT scans, echocardiograms and radioimmune assays, he will also remember to sit at the bedside, to talk and to listen, and to touch.

E. R. W. FOX, MD
Coeur D'Alene, Idaho

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